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(54) Novel peptidase inhibitors.

(57) This invention relates to analogs of peptidase substrates in which the nitrogen atom of the scissile amide gorup of the substrate peptide has been replaced by H or a substituted carbonyl moiety. These analogs of the peptidase substrates provide specific enzyme inhibitors for a variety of proteases, the inhibition of which will have useful physiological consequences in a variety of disease states.

EP 0 363 284 A2

NOVEL PEPTIDASE INHIBITORS

This invention relates to protease enzyme inhibitors useful for a variety of physiological end-use applications.

In its broad aspects, this invention relates to analogs of peptidase substrates in which the nitrogen atom of the scissile amide group of the substrate peptide has been replaced by H or a substituted carbonyl moiety. These analogs of the peptidase substrates provide specific enzyme inhibitors for a variety of proteases, the inhibition of which will have useful physiological consequences in a variety of disease states.

In its more specific aspects, this invention relates to derivatives of certain peptidase substrates which are useful in inhibiting serine-, thio-, carboxylic acid- and metallo-dependent protease enzymes, the inhibition of which will have useful physiological consequences in a variety of disease states.

Still more specifically, this invention relates to derivatives of peptidase substrates which fall within the following generic groupings characterized according to their active site dependencies. Such generic groupings are:

I. Serine Dependent Enzymes: These include such enzymes as Elastase (human leukocyte), Cathepsin G, Thrombin, Plasmin, C-1 Esterase, C-3 Convertase, Urokinase, Plasminogen Activator, Acrosin, β-Lactamase, D-Alanine-D-Alanine Carboxypeptidase, Chymotrypsin, Trypsin and Kallikreins.

II. Thiol Dependent Enzymes: Cathepsin B and Calpain

III. Carboxylic Acid Dependent Enzymes: These include such specific enzymes as Cathepsin D.

IV. Metallo Dependent Enzymes: These include Angiotensin Converting Enzyme, Enkephalinase, Pseudomonas Elastase, Leucine Aminopeptidase and HIV.

The contemplated peptidase inhibitors of the foregoing enzymes are selected from the generic formula

$R_1NHCHR_2C(O)X$

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is H, a protecting group, an α-amino acid or a peptide having 2 to 4 α-amino acids, optionally bearing a protecting group,

R_2 is a residue of an α-amino acid responsible for directing the inhibitor to the active site of the enzyme or is -A-$SiR_7R_8R_9$, C_{1-10} alkyl, aralkyl or aryl, with A being a C_{1-6} alkylene, and each of R_7, R_8 and R_9 being C_{1-10} alkyl, benzyl or phenethyl.

Unless otherwise stated the α-amino acids of the foregoing peptidase substrates are preferably in their L-configuration. A compound of this invention may be in free form, e.g. amphoteric form, or a salt form, e.g., acid addition or anionic salt. A compound may be converted into its salt or base form in an art-known manner, one from another. Preferred salts are trifluoroacetate, hydrochloride, sodium, potassium or ammonium salts, although the scope of salts embraced herein is not limited thereto, the scope being extended to include all of the salts known to be used in the art of peptide chemistry.

As used herein the term "C_{1-10} alkyl" include the straight, branched-chain and cyclized manifestations thereof, particularly such moieties as methyl, ethyl, n-butyl, t-butyl, cyclopropyl, n-propyl, pentyl, cyclopentyl, n-hexyl, n-nonyl, decyl, cyclohexyl and cyclohexylmethyl. The term "aralkyl" includes those aryl moieties attached to a C_{1-4} alkylene. The term "aryl" within the definitions of R_2 and R_3 includes both carbocyclic and heterocyclic moieties. Preferred aralkyl and aryl moieties are phenyl, benzyl, naphthylmethyl, phenethyl, 2-pyridylmethyl, indolyl, pyridyl, indazolyl, furyl and thienyl are preferred. Other carbocyclics are such fused aryl moieties as pentalenyl, indenyl, naphthalenyl, naphthylmethyl, azulenyl, heptalenyl, acenaphthylenyl, fluorenyl, phenalenyl, phenanthrenyl, anthracenyl, acephenanthrylenyl, aceanthrylenyl, triphenylenyl, pyrenyl, chrysenyl and naphthacenyl. In the term "-A-$SiR_7R_8R_9$" the alkylene moiety (i.e. "A") is a straight or branched-chain alkylene moiety separating the "$SiR_7R_8R_9$" moiety from the carbon atom to which the "-A-$SiR_7R_8R_9$" radical is attached. Of the R_7, R_8 and R_9 radicals attached to the silicone atom it is preferred that two or three of these radicals be a C_{1-10} lower alkyl radical (preferably methyl or ethyl) and that when one of them contains an aryl radical it is preferred that that radical be a benzyl or phenethyl radical. It is preferred that the alkylene moiety be methylene. Preferred moieties are trimethylsilyl methyl, triethylsilylmethyl, benzyldiethylsilylmethyl, benzyldimethylsilylmethyl, benzylethylmethylsilylmethyl, and the like.

Before further defining and/or illustrating the scope of the peptidase substrate inhibitors embraced by Formula I, it may be convenient to state some of the more basic concepts related to peptides. For example, except for proline, all of the α-amino acids found in proteins have, as a common denominator, a free carboxyl group and a free unsubstituted amino group on the α-carbon atom (in proline, since proline's α-

amino group is substituted it is really an α-imino acid, but for convenience, it will also be spoken of as an α-amino group). Additionally, each α-amino acid has a characteristic "R-group", the R-group being the side-chain, or residue, attached to the α-carbon atom of the α-amino acid. For example, the R-group residue for glycine is hydrogen, for alanine it is methyl, for valine it is isopropyl. (Thus, throughout this specification the R_2 moiety is the residue R-group for each indicated α-amino acid). For the specific R-groups - or side chains - of the α-amino acids reference to A.L. Lehninger's text on Biochemistry (see particularly Chapter 4) would be helpful.

As a further convenience for defining the scope of the compounds embraced by the generic concept of Formula 1, as well as the sub-generic concepts relating to each of the individual enzymes involved in this invention, various α-amino acids have been classified into a variety of groups which impart similar functional characteristics for each of the specific enzymes to be inhibited by the peptidase substrates of Formula 1. These groups are set forth in Table II and the recognized abbreviations for the α-amino acid blocks are set forth in Table I.

TABLE I

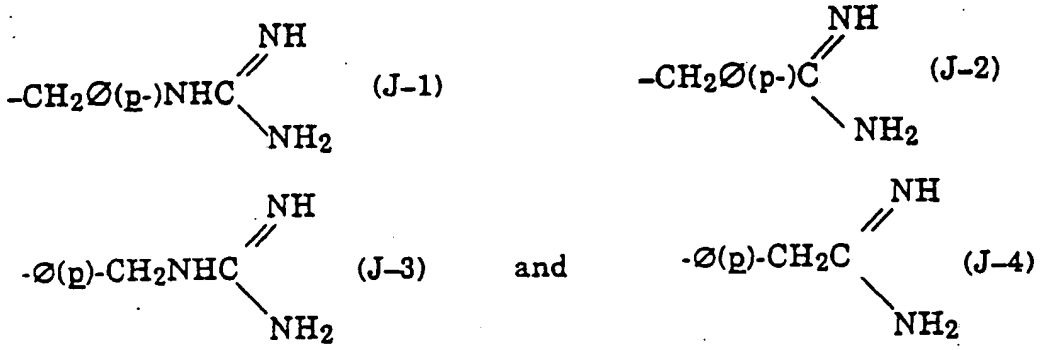
AMINO ACID	SYMBOL
Alanine	Ala
Arginine	Arg
Aspargine	Asn
Aspartic acid	Asp
Asn + Asp	Asx
Cysteine	Cys
Glutamine	Gln
Glutamic acid	Glu
Gln + Glu	Glx
Glycine	Gly
Histidine	His
Isoleucine	Ile
Leucine	Leu
Lysine	Lys
Methionine	Met
Phenylalanine	Phe
Proline	Pro
Serine	Ser
Threonine	Thr
Tryptophan	Trp
Tyrosine	Tyr
Valine	Val
Norvaline	n-Val
Norleucine	n-Leu
1-Naphthylalanine	Nal(1)
2-Indolinecarboxylic acid	Ind
Sarcosin	Sar

TABLE II

Group A: Lys and Arg
B: Glu, Asp
C: Ser, Thr, Gln, Asn, Cys, His, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, and N-methyl derivatives
C′: Ser, Thr, Gln, Asn and Cys, and their N-methyl derivatives
D: Pro, Ind
E: Ala, β-Ala, Leu, Ile, Val, n-Val, β-Val, Met, β-Valine, β-Alanine, n-Leu and n-methyl derivatives (β-representing beta)

E′: Leu, Ile, n-Val, Met, n-Leu, CHM and their N-methyl derivatives
F: Phe, Tyr, O-Methyl Tyrosine, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, Trp, Nal(1), and N-methyl derivatives
F′: Phe, Tyr, O-methyltyrosine, Trp, Nal-(l) and their N-methyl derivatives.
G: Gly, Sar
G′: Gly

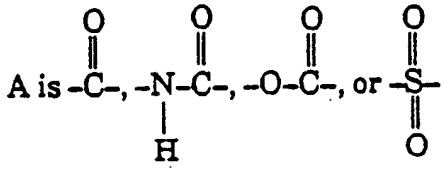
J:



with Ø, of course, representing phenyl (it being understood that the bond of J1-4 is always attached to an amino acid)

K: Acetyl (Ac), Succinyl (Suc), Methoxysuccinyl (H_3COSuc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzoxy (CBZ), Tosyl (Ts), Dansyl (DNS), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulphonyl ($AdSO_2$), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2-CBZ), Phenylacetyl, t-Butylacetyl (Tba), bis [(1-naphthyl)methyl]acetyl (BNMA), or K′

K′: A-Rz wherein



and Rz is an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro,bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido (i.e., acylaminosulfonyl and sulfonylaminocarbonyl) containing form 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro; and such other terminal amino protecting groups which are functionally equivalent thereto.

In those instances wherein the normal R-group residue of an α-amino acid contains an -OH radical (e.g. serine, threonine and tyrosine), it is to be understood that such radical can be derivatized. For example, in each of the foregoing instances the -OH radical can be converted to an ether. When so-converted, such as for example to their methyl ethers, then such radicals will be referred to as O-methyl Ser, O-methyl Thr and O-methyl Tyr, respectively. These methyl ether radicals may also be depicted as $\dot{C}H_2OMe$, $H_3C\dot{H}C$ -OMe and $\dot{C}H_2ø$-OMe(p), respectively. Similarly, other type derivatives will be analogously represented.

In those instances wherein Group K represents an -A-Rz moiety, it is preferred that A represent -C-(=O)- and that Rz represent acylsulfonamido, particularly those wherein the acylsulfonamido contains an aryl moiety (preferably phenyl) substituted by a halogen. The preferred -A-Rz moieties being 4[-(4chlorophenyl)sulfonylaminocarbonyl]phenylcarbonyl, 4[(4bromophenyl)sulfonylaminocarbonyl]-phenylcarbonyl and 4[(phenylsulfonylaminocarbonyl]phenylcarbonyl (said moieties being abbreviated as 4-Cl-ø-SAC-Bz, 4-Br-ø-SAC-Bz and ø-SAC-Bz, respectively).

Quite obviously the modifications to the scissile amide bond of the peptidase substrates of this invention present certain nomenclature difficulties. In order to maintain a general consistency throughout

this application the following explanations are offered to obviate any ambiguities relating to the scope and intent of this invention.

For exemplification, assume R_1 is a dipeptide which contains the two amino acids, Phe and Val, in the P_3 and P_2 positions respectively, the terminal amine of which bears a CBZ moiety of Group K, R_2 is the residue of the P_1-position α-amino acid which in this illustration is Arg. Assume 4 compounds wherein R_3 is either H, methyl, -OH, or OCH_3. In such instances the four different compounds will be written as

CBZ-Phe-Val-Arg[C(O)H],

CBZ-Phe-Val-Arg[C(O)CH_3],

CBZ-Phe-Val-Arg[C(O)-OH],

CBZ-Phe-Val-Arg[C(O)-OCH_3].

The bracketed moiety is used to designate the position wherein the - $\overset{\overset{O}{\|}}{C}$-$R_3$ moiety is located. In those instances wherein the α-amino acid located in any of the indicated P-positions contains an N-alkyl (or other) derivative, then for example in the above illustration of CBZ-Phe-Val-Arg[C(O)-H], if the nitrogen atom of the P_2 position α-amino acid bore a methyl group, then such compound would be indicated as CBZ-Phe-N-Me-Val-Arg[C(O)H]. Of course, it is understood that the designations [C(O)H], [C-(O)CH_3], [C(O)-OH] and [C(O)-OCH_3] indicates the moieties

- $\overset{\overset{O}{\|}}{C}$H, - $\overset{\overset{O}{\|}}{C}$-$CH_3$, - $\overset{\overset{O}{\|}}{C}$-OH and - $\overset{\overset{O}{\|}}{C}$-$OCH_3$,

respectively, which are attached to the carbonyl moiety of the P_1 α-amino acid. In the instance where X is H then, using the foregoing R_1 and R_2 moieties, the compound would be named CBZ-Phe-Val-Arg-H.

In the light of the foregoing the defined compounds of this invention are compounds of the formulae

$R_1NHCHR_2C(O)X$

and

$R_1NHCHR_2CH(OH)X$ I

and hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $C(O)R_3$,

R_1 is H, a Group K protecting group, an α-amino acid, a peptide comprised of 2 to 4 α-amino acids, an α-amino acid bearing a Group K protecting group, or a peptide comprised of 2 to 4 α-amino acids the terminal α-amino acid of which bears a Group K protecting group,

R_2 is the residue of an α-amino acid, C_{1-10} alkyl, aralkyl, aryl or -A-$SiR_7R_8R_9$,

A is a C_{1-6} alkylene, each of

R_7, R_8 and R_9 are C_{1-10} alkyl, benzyl or phenethyl,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy, the said groups of α-amino acids and Group K protecting groups being defined as

A: Lys and Arg

B: Glu, Asp

C: Ser, Thr, Gln, Asn, Cys, His, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, and N-methyl derivatives

C′: Ser, Thr, Gln, Asn and Cys, and their N-methyl derivatives

D: Pro, Ind

E: Ala, β-Ala, Leu, Ile, Val, n-Val, β-Val, Met, β-Valine, β-Alanine, n-Leu and n-methyl derivatives (β-representing beta)

E′: Leu, Ile, n-Val, Met, n-Leu, CHM and their N-methyl derivatives

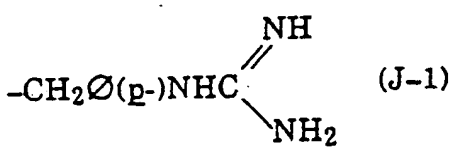
F: Phe, Tyr, O-Methyl Tyrosine, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, Trp, Nal(1), and N-methyl derivatives

F′: Phe, Tyr, O-methyltyrosine, Trp, Nal-(l) and their N-methyl derivatives.

G: Gly, Sar

G′: Gly

J:



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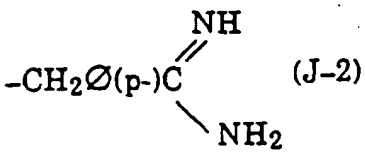

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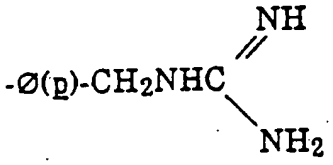
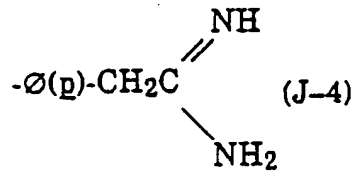


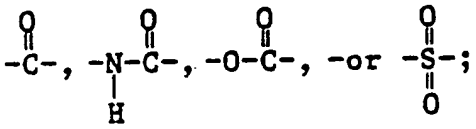
(J-3) and



(J-4)

K: Acetyl (Ac), Succinyl (Suc), Methoxysuccinyl (H_3COSuc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzoxy (CBZ), Tosyl (Ts), Dansyl (DNS), Isovaleryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulphonyl ($AdSO_2$), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2-CBZ), Phenylacetyl, t-Butylacetyl (Tba), bis [(1-naphthyl)methyl]acetyl (BNMA), or K'

K': is -A-Rz wherein A is



and Rz is an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro,bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro.

Compounds of Formula I which are useful as inhibitors of human leucocyte elastase are compounds of the formula

$R_1NHCHR_2C(O)X$ **Ia**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group, preferably MeOSuc, $AdSO_2$, 4-ClØSac-Bz, 4-BrØSac-Bz, ØSac-Bz or 2-CBZ,

P_2 is an α-amino acid of Groups D, E or F, preferably Pro,

P_3 is an α-amino acid of Group E or is deleted, preferably Ala,

P_4 is deleted or an α-amino acid of Group E, preferably Ala,

R_2 is the residue of an α-amino acid of Groups E and G, preferably norvaline or valine.

Human leucocyte elastase is released by polymorphonuclear leukocytes at sites of inflammation and thus is a contributing cause for a number of disease states. Thus the peptidase substrates of formula (Ia) have an antiinflammatory effect useful in the treatment of gout, rheumatoid arthritis and other inflammatory diseases, and in the treatment of emphysema. In their end-use application the enzyme inhibitory properties of the compounds of (Ia) is readily ascertained by standard biochemical technique well known in the art. Potential dose range for their end-use application will of course depend upon the nature and severity of the disease state as determined by the attending diagnostician with the range of 0.01 to 10 mg/kg.body per day being useful for the aforementioned disease state. The preferred compounds for this enzyme are:

MeOSuc-Ala-Ile-Pro-Val[$C(O)CH_3$],

(αN-$AdSO_2$)-(εN-2-CBZ-Lys)-Pro-Val-[$C(O)CH_3$],

4-Cl-Ø-SAC-Bz-Val-Pro-Val-[$C(O)CH_3$],

4-Br-Ø-SAC-Bz-Val-Pro-Val-[$C(O)CH_3$],

Ø-SAC-Bz-Val-Pro-Val-[$C(O)CH_3$],

Br-Ø-SAC-Bz-Val-Pro-Val-[C(O)H],
Cl-Ø-SAC-Bz-Val-Pro-Val-[C(O)H],
Ø-SAC-Bz-Val-Pro-Val-[C(O)H].

Compounds of Formula I which are useful as inhibitors of Cathepsin G are compounds of the formula

$R_1NHCHR_2C(O)X$ **Ib**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is H or $-C(O)R_3$,
R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,
R_1 is $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group, preferably Suc, MeOSuc, Boc, 4-ClØSac-Bz or øSac-Bz,
P_2 is an α-amino acid of Groups D, E and G, preferably Pro,
P_3 is an α-amino acid of Groups E and G, preferably Ala,
P_4 is an α-amino acid of Groups E and G or is deleted, preferably Ala or Val, and
R_2 is the residue of an α-amino acid of Groups E and F, preferably Phe.

The end-use application of the compounds (Ib) inhibiting Cathepsin G is the same as for human leucocyte inhibitors, including arthritis, gout and emphysema, but also embracing the treatment of glomerulonephritis and lung infestations caused by infections in the lung. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ib) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend on the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect. Preferred compounds of formula Ib are:
Suc-Ala-Ala-Pro-Phe-$[C(O)CH_3]$,
Suc-Ala-Ala-Pro-Phe-[C(O)H],
Suc-Ala-Ala-Pro-Phe-[C(O)Et],
Pg * -Ala-Ala-Pro-Phe-$[C(O)CH_3]$,
Pg * -Val-Ala-Pro-Phe-$[C(O)CH_3]$,
Pg * -Ala-Ala-Pro-Phe-[C(O)Et],
Pg * -Ala-Ala-Pro-Phe-[C(O)H].

Compounds of Formula I which are useful as inhibitors of thrombin are compounds of the formula

$R_1NHCHR_2C(O)X$ **Ic**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is H or $-C(O)R_3$,
R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,
R_1 is a Group K protecting group or (a) P_2P_3 or $P_2P_3P_g$ or (b) $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group, preferably the protecting groups are DNS, Ts or Bz,

(a) P_2 is an α-amino acid of Groups D, E and F, preferably Pro, P_3 is an α-amino acid of Group F, preferably in their D-configuration, preferably D-Phe,

(b) P_2 is an α-amino acid of Group E, preferably Ala, P_3 is an α-amino acid of Groups C, G and E, preferably Ser, P_4 is deleted or is an α-amino acid of Groups F, G and E, preferably Phe, and R_2 is the residue of an α-amino acid of Groups A and J, preferably Arg.

The compounds embraced by formula (Ic) inhibit thrombin and therefore, as in the use of heparin, the compounds may be used as the initial anticoagulant agent in thrombophlebitis and coronary thrombosis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ic) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect. Preferred compounds are as expressed for Cathepsin G and also include: H-(D)-Phe-Pro-Arg[C(O)H],
H-(D)-Phe-Pro-Arg$[C(O)CH_3]$,
DNS-Arg-[C(O)H]
H-Phe-Ser-Ala-[C(O)H],
H-Phe-Ser-Ala-$[C(O)CH_3]$,
Bz-Jl-[C(O)H],

*Pg representing 4-Cl or BrØ-SAC-Bz, Ø-SAC-Bz or Boc.

Bz-JI-[C(O)CH_3].

Compounds of Formula I which are useful as inhibitors of chymotrypsin are compounds of the formula

$R_1NHCHR_2C(O)X$ **Id**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $C(O)R_3$ and R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is a Group K protecting group, $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group, preferably R_1 is a Group K protecting group, preferably Bz,

P_2 is an α-amino acid of Groups D, E and G,

P_3 is an α-amino acid of Groups E and G or is deleted, preferably Ala,

P_4 is is an α-amino acid of Groups E and G or is deleted, preferably Ala,

R_2 is a residue of an α-amino acid of Groups E and F, preferably Phe or Tyr.

The end-use application of the compounds of (Id) inhibiting chymotrypsin is in the treatment of pancreatitis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Id) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect. Preferred compounds are as expressed for Cathepsin G and also include:

Bz-Phe-[C(O)H],
Bz-Phe-(C(O)Me],
Bz-Tyr-[C(O)H]
Bz-Tyr-[C(O)Me],
Pg * -Val-Pro-Phe-[C(O)CH_3],
Pg * -Ala-Ala-Phe-[C(O)CH_3].

Compounds of Formula I which are useful as inhibitors of trypsin are compounds of the formula

$R_1NHCHR_2C(O)X$ **Ie**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is a Group K protecting group, or (a) $P_2P_3P_g$ or P_2P_3, or (b) $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group, preferably the protecting group is DNS or tosyl,

(a) P_2 is an α-amino acid of Groups D, E and F, preferably in their D-configuration, preferably D-Phe, P_3 is an α-amino acid of Group F, preferably D-Ala,

(b) P_2 is an α-amino acid of Groups D and E, preferably Pro or Ala, P_3 is an α-amino acid of Groups C, E and G, preferably Ser, P_4 is deleted or is an α-amino acid of Groups C and E, preferably Phe, and R_2 is the residue of an α-amino acid of Groups A or J, preferably Arg.

The end-use application of the compounds (Ie) inhibiting trypsin is in the treatment of pancreatitis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ie) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect. The preferred compounds useful for inhibiting trypsin are the same for the inhibition of thrombin.

Compounds of Formula I which are useful as inhibitors of plasmin are compounds of the formula

$R_1NHCHR_2C(O)X$ **If**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably DNS,

P_2 an α-amino acid of Group F, preferably Phe,

P_3 is an α-amino acid of Groups B and F, preferably Glu, and

R_2 is the residue of an α-amino acid of Groups A and J, preferably Lys.

The compounds embraced by Formula (If) inhibit plasmin and are therefore, antiproliferative agents useful in treating excessive cell growth, particularly in the treatment of benign prostatic hypertrophy and

*Pg being Bz, Boc, 4-Cl or 4-BrØ-SAC-Bz, or Ø-SAC-Bz.

prostatic carcinoma, and in the treatment of psoriasis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (If) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use applciation will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect. Preferred compounds are:

DNS-Glu-Phe-Lys-[C(O)H],

DNS-Glu-Phe-Lys-[C(O)CH_3].

Compounds of Formula I which are useful as inhibitors of C1-esterase are compounds of the formula

$R_1NHCHR_2C(O)X$ **Ig**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or -C(O)R_3,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is P_2 or P_2P_g, P_g being a Group K protecting group, preferably CBZ,

P_2 is an α-amino acid of Groups A, B, C, D, E, F and G, preferably Ala,

R_2 is the residue of an α-amino acid of Groups A and J preferably Arg.

The compounds embraced by Formula (Ig) inhibit C1-esterase and are therefore useful in treating systemic lupus, arthritis, autoimmune hemolytic anemia and glomerulonephritis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ig) is readily ascertained by standard biochemical techniques well known in the art. Actual dose range for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Preferred compounds are:

CBZ-Ala-Arg-[C(O)H],

CBZ-Ala-Arg-[C(O)Me],

CBZ-Ala-(p-gua)Phe-[C(O)H].

Compounds of Formula I which are useful as inhibitors of C3-convertase are compounds of the formula

$R_1NHCHR_2C(O)X$ **Ih**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or -C(O)R_3,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably Bz,

P_2 is an α-amino acid of Groups E or F, preferably Ala,

P_3 is an α-amino acid of Groups E or F, preferably Leu, and

R_2 is the residue of an α-amino acid of Groups A and J, preferably Arg.

The compounds embraced by formula (Ih) inhibit C3-convertase and are therefore useful in treating systemic lupus, arthritis, autoimmune hemolytic anemia and glomerulonephritis. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ih) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

The preferred compounds are:

Bz-Leu-Ala-Arg-[C(O)H],

Bz-Leu-Ala-Arg[C(O)OCH_3],

Bz-Leu-Ala-Arg-[C(O)OH].

Compounds of Formula I which are useful as inhibitors of Urokinase are compounds of the formula

$R_1NHCHR_2C(O)X$ **II**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or -C(O)R_3,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably CBZ,

P_2 is an α-amino acid of Groups E and G, preferable Ala and Gly, and

P_3 is an α-amino acid of Group B, preferably Glu,

R_2 is the residue of an α-amino acid of Groups A and J, preferably Arg or J-1 (i.e., p-guanidine Phe).

Preferred Urokinase inhibitors are:

H-GLu-Gly-Arg[C(O)Me],

H-Glu-Gly-Arg[C(O)H],

H-Gly-Gly-(p-gua)* Phe-[C(O)Me].

The compounds of Formula (Ii) inhibit urokinase and therefore are useful in treating excessive cell growth disease state. As such the compounds are useful in the treatment of benign prostatic hypertrophy and prostatic carcinoma, the treatment of psoriasis, and in their use as abortifacients. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ii) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of plasminogen activator are compounds of the formula

$R_1NHCHR_2C(O)X$ Ij

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably DNS,

P_2 is Gly,

P_3 is an α-amino acid of Group B, preferably Glu, and

R_2 is the residue of an α-amino acid of Groups A and J, preferably Arg or J-1.

Preferred compounds are:

DNS-Glu-Gly-Arg-[C(O)Me],

DNS-Glu-Gly-Arg-[C(O)H],

DNS-Glu-Gly-(p-gua)Phe-[C(O)Et].

The compounds of the Formula (Ij) inhibit plasminogen activator and therefore are useful in treating excessive cell growth disease states. As such the compounds are useful in the treatment of benign prostatic hypertrophy and prostatic carcinoma, in the treatment of psoriasis and in their use as abortifacients. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ij) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of acrosin are compounds of the formula

$R_1NHCHR_2C(O)X$ Ik

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably BOC,

P_2 is an α-amino acid of Group E, preferably Leu,

P_3 is an α-amino acid of Group E, preferably Leu, and

R_2 is the residue of an α-amino acid of Groups A and J, preferably Arg.

Preferred compounds are:

Boc-Leu-Leu-Arg-[C(O)H],

Boc-Leu-Leu-Arg-[C(O)Me].

The compounds of the Formula (Ik) are acrosin inhibitors and therefore are useful as anti-fertility agents in that they possess the characteristics of preventing sperm from penetrating an otherwise fertilizable egg. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ik) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an

*(p-gua)being para-guanidino.

effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of β-Lactamase are compounds of the formulae

$R_1NHCHR_2C(O)X$

and

$R_1NHCHR_2CH(OH)X$ II

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is a Group K protecting group, preferably CBZ or Bz,

R_2 is the residue of an α-amino acid of Groups C, E and G, preferably Gly.

The preferred compounds, preferably in their chemically reduced form, are:

Bz-Gly-[C(O)H],

Bz-Gly-[C(O)Me],

CBZ-Gly-[C(O)H],

CBZ-Gly-[C(O)Me].

The compounds embraced by Formula (II) inhibit β-Lactamase and therefore are useful in the potentiation of antibacterial agents, particularly the β-lactam antibacterials. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (II) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of D-Ala-D-Ala Carboxypeptidase are compounds of the formula

$R_1NHCHR_2C(O)X$ Im

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is P_2 or P_2P_g, P_g being a Group K protecting group, preferably Ac,

P_2 is εN-Ac-Lys or an α-amino acid of Groups C and E, preferably εN-Ac-Lys, and

R_2 is D-Ala.

The preferred compounds are:

$(N\alpha,\epsilon)$-di-Ac-Lys-D-Ala[C(O)H],

$(N\alpha,\epsilon)$-di-Ac-Lys-D-Ala[$C(O)CH_3$].

The compounds embraced by Formula (Im) are antibacterial agents particularly useful against gram negative organisms. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Im) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of Cathepsin B are compounds of the formula

$R_1NHCHR_2C(O)X$ In

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably CBZ or Ac,

P_2 is an α-amino acid of Groups E and F, preferably Phe or Leu,

P_3 is deleted or is an α-amino acid of Groups E and F, preferably Leu or is deleted, and

R_2 is the residue of an α-amino acid of Groups A, E or J or $ThrOCH_2Ø$, preferably Arg or $ThrOCH_2Ø$.

The preferred compounds are:

CBZ-Phe-Thr-[C(O)H]
|
OBz

CBZ-Phe-Thr-[C(O)CH_3]
|
OBz.

The compounds of Formula (In) inhibit Cathepsin B and therefore are useful in treating excessive cell growth disease states such as, for example, being useful in treating benign prostate hypertrophy, prostatic carcinoma, in treating psoriasis and in their use as abortifacients. Additionally, the compounds of (In) are useful as feed additives for cattle. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (In) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of pepsin are compounds of the formulae

$R_1NHCHR_2C(O)X$

and

$R_1NHCHR_2CH(O)X$ **Io**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably Iva,

P_2 is an α-amino acid of Groups E and F, preferably Val,

P_3 is an α-amino acid of Groups E and F, preferably Val,

R_2 is the residue of an α-amino acid of Groups E and F, preferably Leu.

The preferred compound is:

Iva-Val-Val-Leu[C(O)H].

The compounds of Formula (Io) inhibit pepsin and therefore exert and antiulcer effect useful in the treatment and prevention of ulcers. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Io) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of Cathepsin D are compounds of the formula

$R_1NHCHR_2C(O)X$ **Ip**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably CBZ,

P_2 is an α-amino acid of Groups E and F, preferably Val,

P_3 is an α-amino acid of Groups E and F, preferably Val,

R_2 is the residue of an α-amino acid of Groups E and F, preferably Phe.

The preferred compound is:

CBZ-Val-Val-Phe-[C(O)H].

As inhibitors of Cathepsin D the compounds of Formula (Ip) are useful for the same end-use applications set forth for human leukocyte elastase inhibitors (Ia) and are also useful as antidemyelinating agents useful to prevent and arrest nerve tissue damage. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ip) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of enkephalinase are compounds of the formula

$R_1NHCHR_2C(O)X$ **Iq**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably there is no Group K protecting group,

P_2 is Gly,

P_3 is an α-amino acid of Group F or is deleted, preferably Tyr, and

R_2 is Gly.

The preferred compounds are:

Tyr-Gly-Gly[C(O)H]

Tyr-GLy-Gly[C(O)OH].

The compounds of Formula (Iq) inhibit enkephalinase and are therefore useful as analgesics. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Iq) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of Pseudomonas elastase are compounds of the formula

$R_1NHCHR_2C(O)X$ **Ir**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is P_2 or P_2 P_g, P_g being a Group K protecting group, preferably MeOSuc,

and P_2 is an α-amino acid of Group E, preferably Ala,

R_2 is the residue of an α-amino acid of Groups E and G, preferably Ala.

The preferred compounds is:

MeOSuc-Ala-Ala-[C(O)Et].

The compounds of Formula (Ir) inhibit Pseudomonas elastase and therefore are useful as antibacterial agents particularly useful against infections caused by pseudomonas bacteria. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Ir) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of Leucine aminopeptidase are compounds of the formula

$R_1NHCHR_2C(O)X$ **Is**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is H,

R_2 is the residue of an α-amino acid of Groups A, B, E, F and J, preferably Phe, Leu, Glu, Arg or J-1 (p-guanidine Phe).

The preferred compounds are:

H-Leu[C(O)CH3],

H-Val[C(O)CH3],

H-Arg[C(O)H],

H-Arg[C(O)CH3].

The compounds of Formula (Is) are inhibitors of Leucine aminopeptidase and therefore are useful as immunostimulants useful in conjunctive therapy in the treatment with other known anticancer agents. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of (Is) is readily ascertained by standard biochemical techniques well known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and

severity of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of kallikreins, tissue or plasma are compounds of the formula

$R_1NHCHR_2C(O)X$ It

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or -C(O)R_3,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably there is no protecting group,

P_2 is an α-amino acid of Groups E and F, preferably Phe,

P_3 is an α-amino acid of Groups C, E and F, preferably in their D configuration, preferably D-Pro,

R_2 is the residue of an α-amino acid of Group A, preferably Arg.

The preferred compounds are:

D-Pro-Phe-Arg[C(O)H],

D-Pro-Phe-Arg[$C(O)CH_3$].

The compounds of Formula (It) are inhibitors of the kallikreins, tissue or plasma, and therefore inhibit kinin formations. Kinins are generally known to induce pain and vascular permeability associated with inflammation and infection, e.g. bacterial and viral; the inhibition of the kinin formation renders these compounds useful in the alleviation of pain and inflammation. Furthermore, these compounds are useful as male contraceptives in that they will dramatically interfere with normal sperm function. In their end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of Calpain are compounds of the formula

$R_1NHCHR_2C(O)X$ Iu

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or -C(O)R_3,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is a Group K protecting group, P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group, preferably the protecting groups are CBZ, Bz or Ac,

P_2 is an α-amino acid of Groups E and F, preferably Ala, Phe or Lys,

P_3 is deleted or is an α-amino acid of Groups B, E or F, preferably it is deleted,

R_2 is H, the residue of an α-amino acid of Groups E, F and J or -A-Si-$R_7R_8R_9$, C_{1-7} alkyl, benzyl phenethyl, or naphthyl, preferably cyclohexylmethyl (CHM), naphthyl (NAP), trimethylsilylmethyl (TMSM), benzyldimethylsilylmethyl (BDMS-M), Lys or Phe.

Preferred compounds of Formula (Iu) are:

Ac-Ala-Lys[$C(O)OCH_3$],

CBZ-Phe-[$C(O)CH_3$],

CBZ-Val-Phe-[$C(O)OCH_3$],

CBZ-Val-Phe-[$C(O)CH_3$],

CBZ-Val-Phe-[C(O)Et].

By their inhibition of Calpain and cathepsin B proteases the compounds of (Iu) will (a) have an effect on cell motility through the extracellular matrix rendering the compounds useful for treating cancer metastases; (b) have long term changes in regulatory proteins (e.g. down-regulation of protein kinase C and breakdown of the cytoskeleton causing secondary effects on platelet activation such as (for enhancing clot formation) leukocyte degranulation (for treating inflammation and immunological diseases, e.g. arthritis, emphysema, multiple sclerosis, and systemic lupus); (c) have a general intracellular proteolysis, particular muscle cells, causing secondary effect on ischemia/reperfusion cell death, thereby rendering the compounds useful for treating stroke and heart attacks; and (d) will aid in blocking the lysis of red blood cells rendering the compounds useful in the treatment of conditions associated with excessive hemolysis such as in Sickle cell anemia and in kidney dialysis. It is to be expected that the end-use application dose range will be about 0.01 to 10 mg per kg of body weight per day for an effective therapeutic effect.

Compounds of Formula I which are useful as inhibitors of retroviral proteases required for replication are compounds of the formula

$R_1NHCHR_2C(O)X$ Iv

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or -C(O)R_3,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

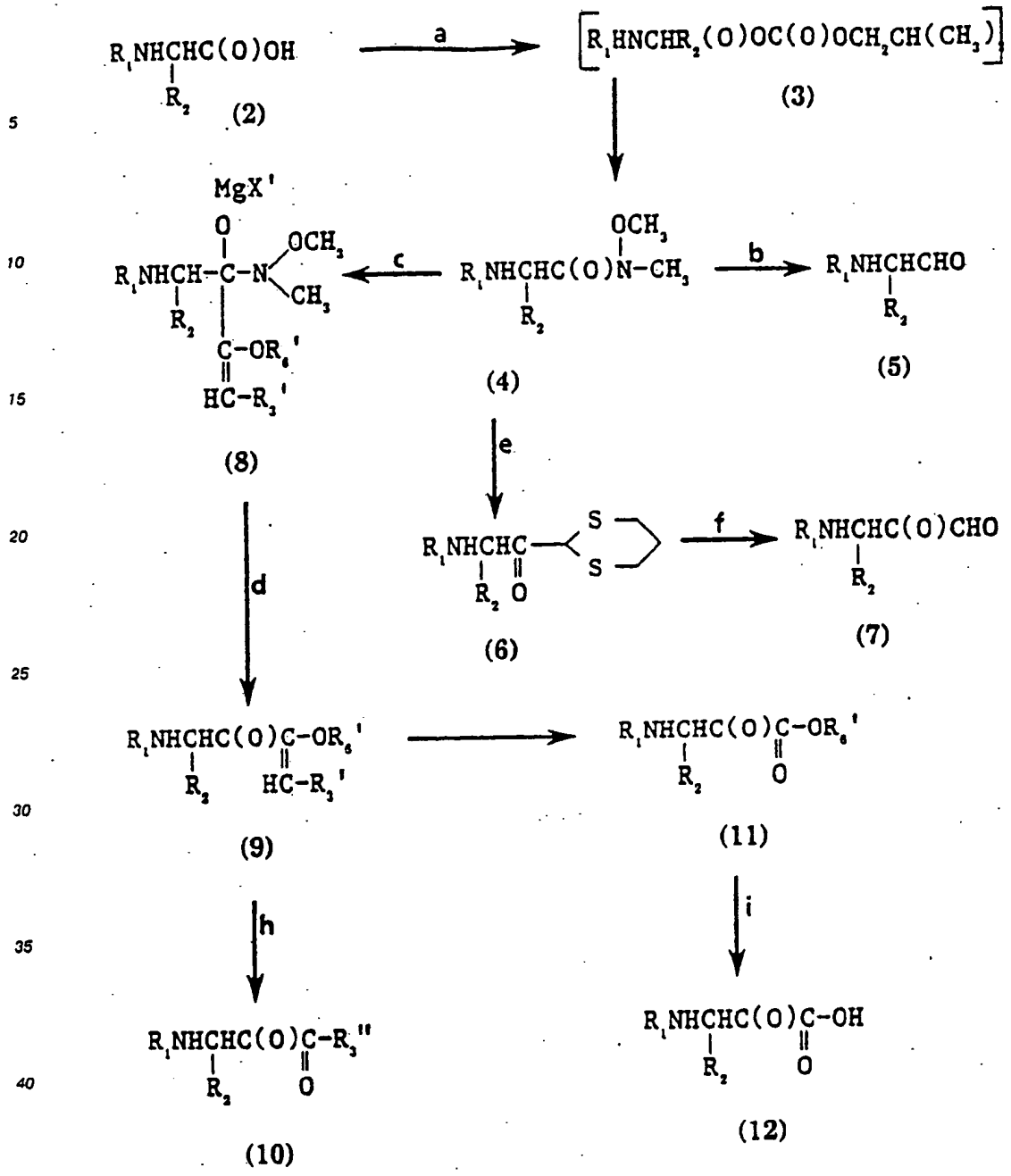
R_1 is $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group, preferably Pg is deleted,

P_2 is an α-amino acid of Groups C′, E′, F′ and G′, preferably Asn, Gln or Ala,
P_3 is an α-amino acid of Groups C′, E′, F′ and G′, preferably Asn, Gln or Ala,
P_4 is an α-amino acid of Group C′, β-Ala or β-Val, preferably Ser or Thr,
R_2 is the residue of an α-amino acid of Groups F′ and E′ or cyclohexylmethyl, preferably Tyr, Phe or CHM.

Preferred compounds of Formula (Iv) are:
Ser-Gln-Asn-Tyr[C(O)OCH_3],
Ser-Gln-Asn-Phe[C(O)OCH_3],
Ser-Leu-Asn-Tyr[C(O)OCH_3],
Ser-Leu-Asn-Phe[C(O)OCH_3],
Ser-Gln-Asn-Tyr[C(O)CH_3],
Ser-Gln-Asn-Phe[C(O)CH_3],
Ser-Leu-Asn-Tyr[C(O)CH_3],
Ser-Leu-Asn-Phe[C(O)CH_3].

In their end-use application in the treatment of retro-viral infections, the compounds of Formula (Iv) will be administered at about 1-100 mg per kg of body weight per day, preferably intravenously.

The preparation of the compounds of this invention may be effected by standard chemical processes analogously known in the art. The processes are depicted and described as follows:



wherein X' is chloro or bromo, R_3' is H or methyl, R_3'' is methyl or ethyl, R_6' is methyl or ethyl and R_1 and R_2 are as previously defined.

In effecting the processes of the foregoing reaction scheme, the starting materials (2) are subjected to process step (a) which is initiated by anionizing the starting material with a base, preferably N-methyl morpholine, triethylamine (TEA), diisopropylethylamine (DIEA) or other suitable amines. Preferably the anion is formed using excess quantities of the amine, stirring the mixture at about -15° C to 10° C, preferably 0° C. Addition of an equivalent amount of isobutylchloroformate with cooling at about -20° C forms an *in situ* mixed anhydride (3). (Other equivalently functioning peptide coupling agents, such as diethylcyanophosphonate, DCC, BOP reagents, BOP chloride, may be used in place of isobutylchloroformate.) Addition of molar equivalent amounts of N,O-dimethylhydroxylamine to the activated *in situ* intermediate (3) yields a dimethylhydroxamic acid derivative (i.e. an N-methyl-N-methoxy amide) of Formula 4. This step, as well as reaction steps (b) and (g), are conducted under an inert atmosphere (argon or nitrogen) under anhydrous conditions.

The hydroxamic derivatives (4) may be chemically reduced step (b) using standard Castro reduction conditions, e.g., lithium aluminum hydride in THF at 0°C or other equivalently functioning reductions, to yield the desired aldehydes (5), or they may be subjected to the reaction conditions of steps (c) and (d) to form compounds 9. Step (c) entails a Grignard reaction using standard reaction conditions such as contacting the reactants together in an inert solvent, preferably tetrahydrofuran, at temperatures of about -20°C to 0°C. The Grignard is freshly prepared from an organo lithium species, e.g., t-butyl lithium added to ethyl vinyl ether which is converted to an ethyl vinyl ether Grignard reagent by reaction with magnesium bromide using standard procedures well known in the art. The hydroxamic derivatives (4) are added to the Grignard reagent to form an *in situ* Grignard complex (8) which, by Step (D), is converted to an α-keto vinyl ether (9), said α-keto vinyl ether being converted by treatment with hydrochloric acid in a dioxane-water mixture or any other inert solvent such as tetrahydrofuran, to the desired diketones of Formula 10.

To obtain the desired α-keto aldehyde of Formula 7, the hydroxamic acid derivatives 4 may be subjected to a nucleophilic attack by 2-metallo-1,3-dithiane according to the techniques of D. Seebach and E.J. Corey [J. Org. Chem., Vol. 40, page 231, (1975)] to form compounds 6. Preferably 2-metallo-1,3-dithiane is formed by addition of a slight excess (5%) of n-butyllithium to a solution of 1,3-dithiane in tetrahydrofuran cooled at -40°C. To this solution is added $\frac{1}{2}$ equivalent of derivatives 4 in an inert solvent and the mixture is stirred at a temperature of about -20°C to 20°C for 1 to 24 hours. The thioketal derivatives 6 may be hydrolyzed to the desired ketoaldehyde derivatives 7 by following standard procedures [J. Org. Chem., 36, 3553 (1971)] such as the use of Lewis acids, $HgCl_2$, or BF_3 etherate, in presence of insoluble base, $Hg\overline{O}$ or CO_3CO_2 in aqueous polar solvents, or the use of oxidative agent, i.e. N-halosuccinimide in aqueous acetonitrile.

To obtain the desired α-keto esters, the ethyl vinyl ethers of Formula 9 are subjected to an ozonolysis (g) which entails treatment with ozone in methylene chloride or other inert solvents at -78°C under an inert atmosphere (N_2 or Ar) to form an *in situ* ozonide which is converted by treatment with dimethylsulfide to form the desired α-keto esters of Formula 11. These compounds (11) may then be subjected to an acid or base catalyzed hydrolysis (preferably LiOH) to produce compounds of Formula 12.

Of course, in those instances wherein it is more convenient for synthesis the compounds of Formulae VII and XI wherein R_1 is a protecting group (preferably BOC) may be prepared by analogous chemical processes and then such compounds would be subjected to solid-phase sequential and block phase synthetic techniques in order to prepare compounds having the requisite R_1 moiety.

The solid phase sequential procedure can be performed using established automated methods such as by use of an automated peptide synthesizer. In this procedure an amino protected amino acid is bound to a resin support at the carboxy terminal end, the amino acid is deprotected at the amino position at which a peptide linkage is desired, the amino group neutralized with a base and the next amino protected amino acid in the desired sequence is coupled in a peptide linkage. The deprotection, neutralization and coupling steps are repeated until the desired polypeptide is synthesized. The compounds of the present invention are thus synthesized from their carboxy terminal end to their amino terminal end. The amino protected amino acid can be a conventional amino acid, a derivative or isomer thereof, or a spacer group. The resin support employed can be any suitable resin conventionally employed in the art for the solid phase preparation of polypeptides. The preferred resin is polystyrene which has been cross-linked with from about 0.5 to about 3% divinyl benzene, which has been either benzhydrylamidated, chloromethylated or hydroxymethylated to provide sites for amide or ester formation with the initially introduced amino protected amino acid.

An example of a hydroxymethyl resin is described by Bodansky et al. [Chem. Ind. (London) 38, 1597-98 (1966)]. The preparation of chloromethyl and benzhhydrylamine resins are described by Stewart et al. ["Solid Phase Peptide Synthesis", 2nd Edition, Pierce Chemical Co., Rockford, Illinois (1984), Chapter 2, pp. 54-55]. Many of these resins are available commercially. In general, the amino protected amino acid which is desired on the carboxy-terminal end of the peptide is bound to the resin using standard procedures and practices as are well known and appreciated in the art. For example, the amino protected amino acid can be bound to the resin by the procedure of Glsin [Helv. Chem. Acta, 56, 1476 (1973)]. When it is desired to use a resin containing a benzhydrylamine moiety as the resin binding site an amino protected amino acid is coupled to the resin through an amide linkage between its α-carboxylic acid and the amino moiety of the resin. This coupling is effected using standard coupling procedures as described below. Many resin-bound amino acids are available commercially.

The α-amino protecting group employed with each amino acid introduced into the polypeptide sequence may be any such protecting group known in the art. Among the classes of amino protecting groups contemplated are: (1) acyl type protecting groups such as formyl, trifluoroacetyl, phthalyl, p-toluenesulfonyl (tosyl), benzenesulfonyl, nitrophenylsulfenyl, tritylsulfenyl, o-nitrophenoxyacetyl, and α-

chlorobutyryl; (2) aromatic urethane type protecting groups such as benzyloxy-carbonyl and substituted benzyloxycarbonyls such as p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α-, α-dimethyl-3,5-dimethoxybennzyloxycarbonyl, and benzhydryloxycarbonyl; (3) aliphatic urethane protecting groups such as tert-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, and allyloxycarbonyl; (4) cycloalkyl urethane type protecting groups such as cyclopentyloxycarbonyl, adamantyloxycarbonyl, and cyclohexyloxycarbonyl; (5) thio urethane type protecting groups such as phenylthiocarbonyl; (6) alkyl type protecting groups such as triphenylmethyl (trityl) and benzyl (Bzl); (7) trialkylsilane protecting groups such as trimethylsilane. The preferred α-amino protecting group is tert-butyloxycarbonyl (Boc). The use of Boc as an α-amino protecting group for amino acids is described by Bodansky et al. in "The Practice of Peptide Synthesis", Springer-Verlag, Berlin (1984), p. 20.

Following the coupling of the amino protected amino acid to the resin support, the α-amino protecting group is removed using any suitable procedure such as by using trifluoroacetic acid, trifluoroacetic acid in dichloromethane, or HCl in dioxane. The deprotection is carried out at a temperature of between 0 °C and room temperature. Other standard cleaving reagents may be used for removal of specific amino protecting groups under conditions well known and appreciated in the art.

After removal and neutralization of the α-amino protecting group the next desired amino-protected amino acid is coupled through a peptide linkage. This deprotection, neutralization and coupling procedure is repeated until a polypeptide of the desired sequence is obtained. Alternatively, multiple amino acid groups may be coupled by the solution method prior to coupling with the resin supported amino acid sequence.

The selection and use of an appropriate coupling reagent is within the skill of the ordinary practitioner in the art. Particularly suitable coupling reagents where the amino acid to be added is Gln, Asn, or Arg or N,N-dicyclohexylcarbodi imide and 1-hydroxybenzotriazole. The use of these reagents prevents nitrile and lactam formation. Other coupling agents are (1) carbodiimides (e.g., N,N-dicyclohexylcarbodiimide and N-ethyl-N′-(γ-dimethylaminopropylcarbodiimide); (3) ketenimines; (4) isoxazolium salts (e.g., N-ethyl-5-phenyl-isoxazolium-3-sulfonate); (5) monocyclic nitrogen containing heterocyclic amides of aromatic character containing one through four nitrogens in the ring such as imidazolides, pyrazolides, and 1,2,4-triazolides (specific heterocyclic amides that are useful include N,N-carbonyldiimidazole and N,N-carbonyl-di-1,2,4-triazole); (6) alkoxylated acetylene (e.g., ethoxyacetylene); (7) reagents which form a mixed anhydride with the carboxyl moiety of the amino acid (e.g., ethylchloroformate and isobutylchloroformate) or the the symmetrical anhydride of the amino acid to be coupled (e.g., Boc-Ala-o-Ala-Boc); (8) nitrogen containing heterocyclic compounds having a hydroxy group on one ring nitrogen (e.g., N-hydroxyphthalimide, N-hydroxysuccinimide, and 1-hydroxybenzotriazole). Other activating reagents and ther use in peptide coupling are described by Kapoor [J. Pharm. Sci., 59, 1-27 (1970)]. The generally preferred coupling method for the amino acids used in the present invention is the use of the symmetrical anhydride as the coupling agent.

The preferred coupling method for Gln, Asn and Arg is to react the protected amino acid, or derivatives or isomers thereof, with N,N-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole (1:1) in N,N-dimethylformamide (DMF) in the presence of the resin or resin-bound amino acid or peptide. The preferred coupling method for other amino acids involves reacting the protected amino acid, or derivative or isomer thereof, with N,N-dicyclohexylcarbodiimide in dichloromethane to form the symmetrical anhydride. The symmetrical anhydride is then introduced into the solid phase reactor containing the resin or resin-bound amino acid or peptide, and the coupling is carried out in a medium of (DMF), or dichloromethane, or DMF: dichloromethane (1:1). A medium of DMF is preferred. The success of the coupling reaction at each stage of the synthesis is monitored by a ninhydrin test as described by Kaiser et al. [Analyt. Biochem. 34, 595 (1970)]. In cases where incomplete coupling occurs, the coupling procedure is repeated. If the coupling is still incomplete, the deprotected amine is capped with a suitable capping reagent to prevent its continued synthesis. Suitable capping reagents and the use thereof are well known and appreciated in the art. Examples of suitable capping reagents are acetic anhydride and acetylimidazole as described by Stewart et al. ["Solid Phase Peptide Synthesis", 2nd Ed., Pierce Chemical Co., Rockford, Ill. (1984), Chapter 2, p. 73].

After the desired amino acid sequence has been obtained, the peptide is cleaved form the resin. This can be effected by procedures which are well known and appreciated in the art, such as by hydrolysis of the ester or amide linkage to the resin. It is preferred to cleave the peptide form the benzhydrylamine resin with a solution of dimethyl sulfide, p-cresol, thiocresol, or anisole in anhydrous hydrogen fluoride. The cleavage reaction is preferably carried out at temperatures between about 0 °C and about room temperature, and is allowed to continue preferably from between about 5 minutes to about 5 hours.

As is known in the art of solid phase peptide synthesis, many of the amino acids bear side chain functionalities requiring protection during the preparation of the peptide. The selection and use of an

appropriate protecting group for these side chain functionalities is within the ability of those skilled in the art and will depend upon the amino acid to be protected and the presence of other protected amino acid residues in the peptide. The selection of such a side chain protecting group is critical in that it must not be removed during the deprotection and coupling steps of the synthesis. For example, when Boc is used as the α-amino protecting group, the following side chain protecting groups are suitable: p-toluenesulfonyl (tosyl) moieties can be used to protect the amino side chains of amino acids such as Lys and Arg; p-methylbenzyl, acetamidomethyl, benzyl (Bzl), or t-butylsulfonyl moieties can be used to protect the sulfide containing side chains of amino acids such as cysteine, homocysteine, penicillamine and the like or derivatives thereof; benzyl (Bzl) or cyclohexyl ester moieties can be used to protect carboxylic acid side chains of amino acids such as Asp, Glu; a benzyl (Bzl) ether can be used to protect the hydroxy containing side chains of amino acids such as Ser and Thr; and a 2-bromocarbobenzoxy (2Br-Z) moiety can be used to protect the hydroxy containing side chains of amino acids such as Tyr. These side chain protecting groups are added and removed according to standard practices and procedures well known in the art. It is preferred to deprotect these side chain protecting groups with a solution of anisole in anhydrous hydrogen fluoride (1:10). Typically, deprotection of side chain protecting groups is performed after the peptide chain synthesis is complete but these groups can alternatively be removed at any other appropriate time. It is preferred to deprotect these side chains at the same time as the peptide is cleaved from the resin.

The compounds are then isolated and purified by standard techniques. The desired amino acids, derivatives and isomers thereof can be obtained commercially or can be synthesized according to standard practices and procedures well known in the art.

The following specific examples are given to illustrate the preparation of this invention although the scope of compounds is meant to be limiting to the scope of compounds embraced by formula I.

EXAMPLE 1

Carbamic acid, [1-[[[3-ethoxy-2-oxo-1-(phenylmethyl)-3-butenyl]amino]carbonyl]-2-methylpropyl]-, phenylmethyl ester

A solution of ethylvinylether (3 ml) in tetrahydrofuran (20 ml) was cooled to -78° C and t-butyllithium (10 ml, 17 mmol, 1.7 M in pentane) was added. The mixture was warmed to 0° C and stirred 0.75 h. To the mixture magnesium bromide etherate (4.38 g, 17 mmol) was added followed by stirring for 5 min. To the mixture, a solution of L-phenylalaninamide, N-[(phenylmethoxy)carbonyl]-L-valyl-N-methoxy-N-methyl (1.75 g, 3.98 mmol) dissolved in tetrahydrofuran (5 ml) was addded and the mixture was stirred for 1.5 h. The reaction mixture was poured into dil. NH_4Cl and the aqueous phase was extracted with ethylacetate (3 x 75 ml). The combined organic extracts were washed with dil. $NaHCO_3$ and dried over Na_2SO_4. The removal of solvent *in vacuo* yielded 1.7 g crude product. The product was purified by recrystallization from 40% EtOAc/hexane-recovery 1.1 g.

EXAMPLE 2

Carbamic acid, [1-[[[2,3-dioxo-1-(phenylmethyl)-butyl]amino] carbonyl]-2-methylpropyl]-, phenylmethyl ester

To a solution of carbamic acid, [1-[[[3-ethoxy-2-oxo-1-(phenylmethyl)-3-butenyl]amino]carbonyl]-2-methylpropyl]-, phenylmethyl ester, steroisomer (300 mg) in 5:1 dioxane/H_2O (10 ml), conc. HCl was added. The mixture was stirred for 24 h at room temperature, poured into dil. $NaHCO_3$ and extracted with ethyl acetate (3 x 50 ml). The combined extracts were dried over Na_2SO_4 and the removal of solvent *in vacuo* gave 330 g of crude product. The product was purified by flash chromatography (30% EtOAc/hexane) to yield 210 mg of the expected product.

EXAMPLE 3

L-Phenylalaninamide, N-[(phenylmethoxy)carbonyl]-L-valyl-N-methoxy-N-methyl

To a suspension of L-phenylalanine, N-[N-[(phenylmethoxy) carbonyl]-L-valyl] (2.5 g, 6.25 mmol) in methylene chloride (25 ml), N-methylmorpholine (1.5 ml) was added. The solution was cooled to -15°C, followed by the addition of isobutylchloroformate (0.8 ml). The solution was stirred for 20 min and N'O-dimethylhydroxylamine HCl (1.0 g) was added. The solution was stirred at -15°C for 1 h, allowed to warm to room temperature and stirred for an additional 3 h. The reaction mixture was poured into dil. $NaHCO_3$ and extracted with ethyl acetate (3 x 75 ml). The combined extracts were dried over Na_2SO_4, the solvent was removed *in vacuo* and the crude product was loaded onto a silica gel column for purification. The expected product was eluted with 75% EtOAc/hexane to yield 1.8 g.

EXAMPLE 4

L-N-(phenylmethoxy)carbonyl-phenylalaninamide-N'-methoxy-N'-methyl

To a solution of L-N-(phenylmethoxy)carbonyl-phenylalanine (25 g, 0.084 mol) in methylene chloride (300 ml), N-methylmorpholine (18.4 ml, 0.167 mol) was added. The mixture was cooled to -15°C and isobutylchloroformate (10.8 ml, 83.6 mmol) was added. The mixture was stirred at -15°C for 15 min followed by the addition of N,O-dimethylhydroxylamine HCl (8.5 g). The mixture was stirred at -15°C for 1 h, allowed to warm to room temperature and stirred for 3 h. The reaction mixture was poured into H_2O (300 ml) and the aqueous phase was extracted with methylene chloride (2 x 150 ml). The combined organic extracts were dried over Na_2SO_4, the volume was reduced to 100 ml and filtered through silica gel (2 inch). The silica gel was washed with methylene chloride (200 ml) and the solvent was removed from the combined filtrates to yield 26.14 g of the expected product.

EXAMPLE 5

2-Ethoxy-5-phenyl-4-[(phenylmethoxy)carbonyl]amino-3-oxo-1-pentene

A solution of ethylvinylether (1.38 ml, 14.5 mmol) in tetrahydrofuran (40 ml) was cooled to -78°C and t-butyllithium (8.53 ml, 14.5 mmol, 1.7 M in pentane) was added. The mixture was warmed to 0°C, stirred for 45 min, cooled to -30°C and magnesium bromide etherate (3.74 g, 14.5 mmol) was added. The mixture was warmed to 0°C over a 15 min period followed by the addition of L-N-(phenylmethoxy)carbonyl-phenylalaninamide-N'-methoxy-N'-methyl (1.0 g, 2.9 mmol). The mixture was allowed to warm to room temperature and stirred for 3 h. The mixture was poured into dil. NH_4Cl and extracted with diethylether (3 x 100 ml). The combined extracts were dried over Na_2SO_4 and the removal of solvent yielded 0.8 g crude product. The crude product (600 mg) was loaded onto silica gel and elution with 20% EtOAc/hexane yielded 410 mg of the expected product.

EXAMPLE 6

2,3-Dioxo-5-phenyl-4-[(phenylmethoxy)carbonyl]amino pentane

To a solution of 2-ethoxy-5-phenyl-4-[(phenylmethoxy) carbonyl]amino-3-oxo-2-penten (100 mg) in methanol (10 ml), concentrated HCl (0.1 ml) was added. The mixture was stirred for 24 h, poured into H_2O and $NaHCO_2$ was added. The aqueous phase was extracted with ethyl acetate (3 x 50 ml). The combined

organic extracts were dried over Na_2SO_4 and removal of solvent *in vacuo* yielded 95 mg crude product. The product was purified by flash chromatography (30% EtOAc/ hexane) to yield 65 mg of the expected product.

EXAMPLE 7

Carbamic acid, [5-[[(1,1-dimethylethoxy)carbonyl]amino]-6-(methoxymethylamino)-6-oxohexyl], phenylmethyl ester

A solution of L-lysine, N^2-[(1,1-dimethylethoxy)carbonyl]-N^6-[(phenylmethoxy)carbonyl] (10 g, 26.3 mmol) in methylene chloride was cooled to 0° C and diisopropylethylamine (9.15 ml) was added. To the mixture isobutylchloroformate (3.4 ml, 26.3 mmol) was added, followed by cooling to -15° C, stirring for 15 min, followed by the addition of N,O-dimethylhydroxylamine HCl (2.7 g). The mixture was stirred at -15° C for 2 h, allowed to warm to room temperature and stirred for 18 h. The reaction mixture was poured into H_2O (200 ml) and extracted with methylene chloride (2 x 150 ml). The combined extracts were dried over $MgSO_4$ and removal of solvent *in vacuo* yielded 13.5 g crude product. The crude product (3.0 g) was loaded onto silica gel for purification. Elution with 50% EtOAc/ hexane afforded 2.01 g of the expected product.

EXAMPLE 8

Carbamic acid, [5-[(1,1-dimethylethoxy)carbonyl]amino]-7-ethoxy-6-oxo-7-octenyl], phenylmethyl ester

A solution of ethylvinylether (2 ml) in tetrahydrofuran was cooled to -78° C and t-butyllithium (12 ml, 20.4 mmol, 1.7 M in pentane) was added. The mixture was stirred at -78° C for 1 h, warmed to 0° C and stirred for 1 h. To the mixture magnesium bromide etherate (5.33 g, 20.6 mmol) was added followed by stirring for 15 min and then the addition of carbamic acid, [5-[[(1,1-dimethylethoxy)carbonyl]amino]-6-(methoxymethylamino)-6-oxohexyl]-, phenylmethyl ester (1.75 g). The mixture was stirred for 1 h at 0° C, poured into dil. NH_4Cl and extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were washed with $NaHCO_3$, H_2O and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was loaded onto silica gel for purification. Elution with 50% EtOAc/hexane afforded 0.97 g of the expected product.

EXAMPLE 9

7-(Phenylmethoxycarbonylamino)-3-[(1,1-dimethylethoxy)carbonylamino]-2-oxo-heptanoic acid ethyl ester

A solution of carbamic acid, [5-[(1,1-dimethylethoxy) carbonyl]amino]-7-ethoxy-6-oxo-7-octenyl], phenylmethyl ester, (2S) (100 mg) in CH_2Cl_2/methanol (25/1 ml) was cooled to -78° C and ozone was bubbled through until the appearance of a blue color. Oxygen was bubbled through to dissipate excess ozone followed by the addition of dimethylsulfide (100 mg). The mixture was poured into H_2O and extracted with CH_2Cl (2 x 40 ml). The combined extracts were dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was loaded onto silica gel for purification. Elution with 50% EtOAc/hexane yielded 45 mg of the expected product.

EXAMPLE 10

L-Phenylalaminal, N[(phenylmethoxy)carbonyl]-L-valyl

A solution of L-phenylalaninamide, N[(phenyl-methoxy) carbonyl]-L-valyl-N′-methoxy-N′-methyl (3 g, 6.8 mol) in tetrahydrofuran (50 ml) was cooled to 0 ° C and LAH (250 mg) was added. The mixture was stirred at 0 ° C for 30 min and quenched by the addition of 10% potassium hydrogen sulfate. The mixture was poured into H_2O (400 ml) and the aqueous phase was extracted with ethyl acetate (3 x 150 ml). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was loaded onto silica gel for purification and the product was eluted with 55% EtOAc/hexane to yield 1.6 g of the expected compound.

EXAMPLE 11

2-[L-N-(Phenylmethoxycarbonyl)amino)phenylalaninyl]-1,3-dithiane

To a solution of 1,3-dithiane (6.0 g, 0.05 mol) in tetrahydrofuran (150 ml) at -30 ▮ C, n-butyllithium (27.5 ml of 2.0 M n-butyllithium in pentane, 0.055 mol) is added. The mixture is stirred for 2 h and L-N-[-(phenylmethoxy)carbonyl]-N′-methoxy-N′-methylphenylalaninamide (3.42 g, 10.0 mmol) is dissolved in tetrahydrofuran (15 ml) and added. The reaction mixture is stirred at 0 ▮ C for 24 h, poured into H_2O and extracted with diethyl ether. The combined organic extracts are washed with H_2O, saturated NaCl and dried over Na_2SO_4. The solvent is removed *in vacuo* and the crude product is purified by flash chromatography on silica gel.

EXAMPLE 12

3-[((Phenylmethoxy)carbonyl)amino]-4-phenyl-2-oxobutyraldehyde

To a solution of 2-[L-N-(phenylmethoxycarbonyl)amino) phenylalaninyl]-1,3-dithiane (387 mg, 1.0 mmol) in a mixture of acetonitrile/H_2O (9:1) (10 ml), bis (trifluoroacetoxy)iodobenzene (644 mg, 1.5 mmol) is added. The reaction mixture is stirred at room temperature until completion as determined by thin layer chromatography, poured into saturated aqueous sodium bicarbonate and extracted with diethyl ether. The combined organic extracts are dried over Na_2SO_4, the solvent is removed *in vacuo* and the crude product is purified by flash chromatography on silica gel.

EXAMPLE 13

2-Oxo-3-[((Phenylmethoxy)carbonyl)amino]-4-phenylbutyric acid

2-Oxo-3-[((phenylmethoxy)carbonyl)amino]-4-phenylbutyric acid ethyl ether (355 mg, 1.0 mmol) in a mixture of dioxane/H_2O is dissolved (10:1, 20 ml) and LiOH (72 mg, 3.0 mmol) is added. The mixture is stirred for 5 h, poured into dilute HCl and extracted with diethyl ether. The combined organic extracts are dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product is purified by flash chromatography on silica gel.

The foregoing describes in detail the generic and specific aspects of the scope of the invention as well as the manner of making and using the invention. In addition thereto, although such procedures are known in the art, references setting forth state of the art procedures by which the compounds may be evaluated for their biochemical effects is also included herein.

For example, human elastase is assayed *in vitro* using chromophoric peptides, succinylalanylalanylalanyl-p-nitro-anilide, methoxysuccinylalanylalanylprolylvalyl-p-nitroanilide, and others, all of which are available commercially. The assay buffer, pH 8.0, and assay techniques are similar to those descirbed by Lottenberg et al. Enzyme is purified from human sputum, although recently it has become commercially available. Kinetic characterization of immediate inhibitors is by means of the Dixon plot, whereas the characterization of slow- and/or tight-binding inhibitors used data analysis techniques reviewed by Williams and Morrison.

Similarly, the other proteases are assayed and effects of inhibitors are assessed *in vitro* by similar spectroscopic techniques: cathepsin G; thrombin; chymotrypsin; trypsin; plasmin; Cl-esterase; urokinase; plasminogen activator; acrosin; β-lactamase; cathepsin B; pepsin; cathepsin D and leucine aminopeptidase. Pseudomonas elastase is measured in a coupled assay procedure using a human leastase substrate and microsomal aminopeptidase.

Radiometric assays of angiotensin I-converting enzyme and enkephalinase and their inhibitors are based on the procedure of Ryan and use tritiated substrate purchased from Ventrex Laboratories, Inc. Radioimmunoassay is used for studies with renin. C3-convertase is measured as described by Tack et al.

By following the technique referred above, as well as by utilization of other known techniques, as well as by comparison with compounds known to be useful for treatment of the above-mentioned disease states, it is believed that adequate material is available to enable one of ordinary skill in the art to practice the invention. Of course, in the end-use application of the compounds of this invention, the compounds are preferably formulated into suitable pharmaceutical preparations such as tablets, capsules or elixers, for oral administration or in sterile solutions or suspensions for parenteral administration. The compounds of this invention can be administered to patients (animals and human) in need of such treatment in a dosage range of 0.01-10 mg per kg of body weight per day. As stated above, the dose will vary depending on severity of disease, weight of patient and other factors which a person skilled in the art will recognize.

Typically the compounds described above are formulated into pharmaceutical compositions as discussed below.

About 10 to 500 mg of a compound or mixture of compounds of Formula I or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, perservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

Illustrative of the adjuvants which may be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contian in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc. or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like can be incorporated as required.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

Claims

1. A compound of the formulae

$R_1NHCHR_2C(O)X$

and

$R_1NHCHR_2CH(OH)X$ I

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $C(O)R_3$,

R_1 is H, a Group K protecting group, an α-amino acid, a peptide comprised of 2 to 4 α-amino acids, an α-amino acid bearing a Group K protecting group, or a peptide comprised of 2 to 4 α-amino acids the terminal α-amino acid of which bears a Group K protecting group,

R_2 is the residue of an α-amino acid, C_{1-10} alkyl, aralkyl, aryl or -A-$SiR_7R_8R_9$,

A is a C_{1-6} alkylene each of

R_7, R_8 and R_9 are C_{1-10} alkyl, benzyl or phenethyl,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

the said groups of α-amino acids and Group K protecting groups being defined as

A: Lys and Arg

B: Glu, Asp

C: Ser, Thr, Gln, Asn, Cys, His, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, and N-methyl derivatives

C′: Ser, Thr, Gln, Asn and Cys, and their N-methyl derivatives

D: Pro, Ind

E: Ala, β-Ala, Leu, Ile, Val, n-Val, β-Val, Met, β-Valine, β-Alanine, n-Leu and n-methyl derivatives (β-representing beta)

E′: Leu, Ile, n-Val, Met, n-Leu, CHM and their N-methyl derivatives

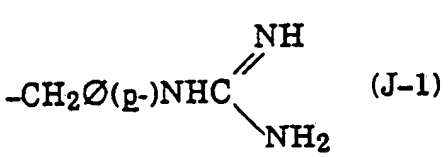
F: Phe, Tyr, O-Methyl Tyrosine, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, Trp, Nal(1), and N-methyl derivatives

F′: Phe, Tyr, O-methyltyrosine, Trp, Nal-(l) and their N-methyl derivatives.

G: Gly, Sar

G′: Gly

J: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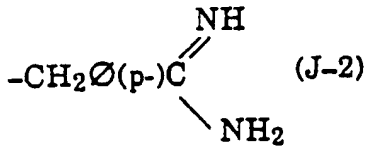
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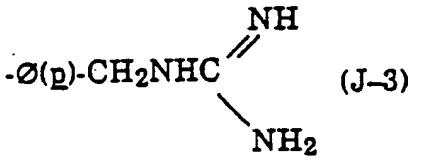
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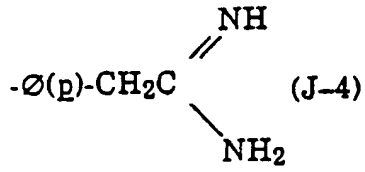
and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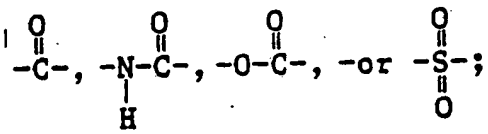
K: Acetyl (Ac), Succinyl (Suc), Methoxysuccinyl (H_3COSuc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzoxy (CBZ), Tosyl (Ts), Dansyl (DNS), Iso-valeryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulphonyl ($AdSO_2$), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2-CBZ), Phenylacetyl, t-Butylacetyl (Tba), bis [(1-naphthyl)methyl]acetyl (BNMA), or K′

K′: is -A-Rz wherein A is



and Rz is an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro.

2. Compounds of Claim 1 of the formula

$R_1NHCHR_2C(O)X$ **Ia**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group,

P_2 is an α-amino acid of Groups, D, E or F,

P_3 is an α-amino acid of Group E or is deleted,

P_4 is deleted or an α-amino acid of Group E,

R_2 is the residue of an α-amino acid of Groups E and G.

3. A compound of Claim 2, said compound being MeOSuc-Ala-Ile-Pro-Val[$C(O)CH_3$],

(αN-$AdSO_2$)-(εN-2-CBZ-Lys)-Pro-Val-[$C(O)CH_3$],

4-Cl-Ø-SAC-Bz-Val-Pro-Val-[$C(O)CH_3$],

4-Br-Ø-SAC-Bz-Val-Pro-Val-[$C(O)CH_3$],

Ø-SAC-Bz-Val-Pro-Val-[$C(O)CH_3$],

Br-Ø-SAC-Bz-Val-Pro-Val-[C(O)H],

Cl-Ø-SAC-Bz-Val-Pro-Val-[C(O)H],

Ø-SAC-Bz-Val-Pro-Val-[C(O)H].

4. Compounds of Claim 1 of the formula

$R_1NHCHR_2C(O)X$ **Ib**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group,

P_2 is an α-amino acid of Groups D, E and G,

P_3 is an α-amino acid of Groups E and G,

P_4 is an α-amino acid of Groups E and G or is deleted, and

R_2 is the residue of an α-amino acid of Groups E and F.

5. A compound of Claim 4, said compound being

Suc-Ala-Ala-Pro-Phe-[$C(O)CH_3$],

Suc-Ala-Ala-Pro-Phe-[C(O)H],

Suc-Ala-Ala-Pro-Phe-[C(O)Et],

Pg * -Ala-Ala-Pro-Phe-[$C(O)CH_3$],

Pg * -Val-Ala-Pro-Phe-[$C(O)CH_3$],

Pg * -Ala-Ala-Pro-Phe-[C(O)Et],

Pg * -Ala-Ala-Pro-Phe-[C(O)H].

6. Compounds of Claim 1 of the formula

$R_1NHCHR_2C(O)X$ **Ic**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is a Group K protecting group or (a) P_2P_3 or $P_2P_3P_g$ or (b) $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group,

(a) P_2 is an α-amino acid of Groups D, E and F, P_3 is an α-amino acid of Group F,

(b) P_2 is an α-amino acid of Group E, P_3 is an α-amino acid of Groups C, G and E, P_4 is deleted or is an α-amino acid of Groups F, G and E,

R_2 is the residue of an α-amino acid of Groups A and J.

7. A compound of Claim 6, said compound being

H-(D)-Phe-Pro-Arg[C(O)H],

H-(D)-Phe-Pro-Arg[$C(O)CH_3$],

DNS-Arg-[C(O)H]

H-Phe-Ser-Ala-[C(O)H],

H-Phe-Ser-Ala-[$C(O)CH_3$],.

Bz-Jl-[C(O)H],

Bz-Jl-[$C(O)CH_3$].

8. Compounds of Claim 1 of the formula

*Pg representing 4-Cl or BrØ-SAC-Bz, Ø-SAC-Bz or Boc.

$R_1NHCHR_2C(O)X$ **Id**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is H or $C(O)R_3$ and R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,
R_1 is a Group K protecting group, $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group,
P_2 is an α-amino acid of Groups D, E and G,
P_3 is an α-amino acid of Groups E and G or is deleted,
P_4 is is an α-amino acid of Groups E and G or is deleted,
R_2 is a residue of an α-amino acid of Groups E and F.

9. A compound of Claim 8, said compound being Bz-Phe-[C(O)H],
Bz-Phe-[C(O)Me],
Bz-Tyr-[C(O)H]
Bz-Tyr-[C(O)Me],
Pg * -Val-Pro-Phe-[$C(O)CH_3$],
Pg * -Ala-Ala-Phe-[$C(O)CH_3$].

10. Compounds of Claim 1 of the formula

$R_1NHCHR_2C(O)X$ **Ie**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is H or $-C(O)R_3$,
R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,
R_1 is a Group K protecting group, or (a) $P_2P_3P_g$ or P_2P_3, or (b) $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group,
(a) P_2 is an α-amino acid of Groups D, E and F, P_3 is an α-amino acid of Group F,
(b) P_2 is an α-amino acid of Groups D and E,
P_3 is an α-amino acid of Groups C, E and G,
P_4 is deleted or is an α-amino acid of Groups C and E, and
R_2 is the residue of an α-amino acid of Groups A or J.

11. A compound of Claim 10, said compound being
H-(D)-Phe-Pro-Arg[C(O)H],
H-(D)-Phe-Pro-Arg[$C(O)CH_3$],
DNS-Arg-[C(O)H]
H-Phe-Ser-Ala-[C(O)H],
H-Phe-Ser-Ala-[$C(O)CH_3$],
Bz-Jl-[C(O)H],
Bz-Jl-[$C(O)CH_3$].

12. Compounds of Claim 1 of the formula

$R_1NHCHR_2C(O)X$ **If**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is H or $-C(O)R_3$,
R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,
R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group,
P_2 an α-amino acid of Group F,
P_3 is an α-amino acid of Groups B and F, and
R_2 is the residue of an α-amino acid of Groups A and J.

13. A compound of Claim 12, said compound being
DNS-Glu-Phe-Lys-[C(O)H],
DNS-Glu-Phe-Lys-[$C(O)CH_3$].

14. Compounds of Claim 1 of the formula

$R_1NHCHR_2C(O)X$ **Ig**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is H or $-C(O)R_3$,
R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,
R_1 is P_2 or P_2P_g, P_g being a Group K protecting group,
P_2 is an α-amino acid of Groups A, B, C, D, E, F and G,
R_2 is the residue of an α-amino acid of Groups A and J.

15. A compound of Claim 14, said compound being
CBZ-Ala-Arg-[C(O)H],

*Pg being Bz, Boc, 4-Cl or 4-BrØ-SAC-Bz, or Ø-SAC-Bz.

CBZ-Ala-Arg-[C(O)Me].
CBZ-Ala-(p-gua)Phe-[C(O)H].

16. Compounds of Claim 1 of the formula

$R_1NHCHR_2C(O)X$ **Ih**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is H or -C(O)R_3,
R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,
R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group,
P_2 is an α-amino acid of Groups E or F,
P_3 is an α-amino acid of Groups E or F, and
R_2 is the residue of an α-amino acid of Groups A and J.

17. A compound of Claim 16, said compound being

Bz-Leu-Ala-Arg-[C(O)H],
Bz-Leu-Ala-Arg[C(O)OCH_3],
Bz-Leu-Ala-Arg-[C(O)OH].

18. Compounds of Claim 1 of the formula

$R_1NHCHR_2C(O)X$ **Ii**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is H or -C(O)R_3,
R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,
R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group,
R_2 is an α-amino acid of Groups E and G, and
P_3 is an α-amino acid of Group B,
R_2 is the residue of an α-amino acid of Groups A and J.

19. A compound of Claim 18, said compound being

H-Glu-Gly-Arg[C(O)Me],
H-Glu-Gly-Arg[C(O)H],
H-Gly-Gly-(p-gua) * Phe-[C(O)Me].

20. Compounds of Claim 1 of the formula

$R_1NHCHR_2C(O)X$ **Ij**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is H or -C(O)R_3,
R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,
R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group,
P_2 is Gly,
P_3 is an α-amino acid of Group B, and
R_2 is the residue of an α-amino acid of Groups A and J.

21. A compound of Claim 20, said compound being

DNS-Glu-Gly-Arg-[C(O)Me],
DNS-Glu-Gly-Arg-[C(O)H],
DNS-Glu-Gly-(p-gua)Phe-[C(O)Et].

22. Compounds of Claim 1 of the formula

$R_1NHCHR_2C(O)X$ **Ik**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is H or -C(O)R_3,
R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,
R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group,
P_2 is an α-amino acid of Group E,
P_3 is an α-amino acid of Group E, and
R_2 is the residue of an α-amino acid of Groups A and J.

23. A compound of Claim 22, said compound being

Boc-Leu-Leu-Arg-(C(O)H],
Boc-Leu-Leu-Arg-[C(O)Me].

24. Compounds of Claim 1 of the formulae

$R_1NHCHR_2C(O)X$
and

*(p-gua) being para -guanidino.

$R_1NHCHR_2CH(OH)X$ **II**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is a Group K protecting group,

R_2 is the residue of an α-amino acid of Groups C, E and G

25. A compound of Claim 24, said compound being

Bz-Gly-[C(O)H],

Bz-Gly-[C(O)Me],

CBZ-Gly-[C(O)H],

CBZ-Gly-[C(O)Me].

26. Compounds of Claim 1 of the formula

$R_1NHCHR_2C(O)X$ **Im**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is P_2 or P_2P_g, P_g being a Group K protecting group,

P_2 is εN-Ac-Lys or an α-amino acid of Groups C and E, and

R_2 is D-Ala.

27. A compound of Claim 26, said compound being

(Nα,ε)-di-Ac-Lys-D-Ala[C(O)H],

(Nα,ε)-di-Ac-Lys-D-Ala[$C(O)CH_3$].

28. Compounds of Claim 1 of the formula

$R_1NHCHR_2C(O)X$ **In**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

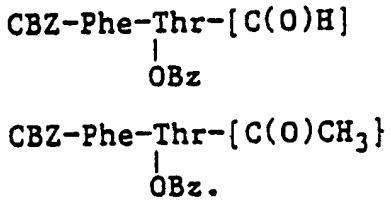
R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group,

P_2 is an α-amino acid of Groups E and F,

P_3 is deleted or is an α-amino acid of Groups E and F, and

R_2 is the residue of an α-amino acid of Groups A, E or J or $ThrOCH_2Ø$.

29. A compound of Claim 28, said compound being



30. Compounds of Claim 1 of the formulae

$R_1NHCHR_2C(O)X$

and

$R_1NHCHR_2CH(OH)X$ **Io**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $-C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group,

P_2 is an α-amino acid of Groups E and F,

P_3 is an α-amino acid of Groups E and F,

R_2 is the residue of an α-amino acid of Groups E and F.

31. A compound of Claim 30, said compound being

Iva-Val-Val-Leu[C(O)H].

32. Compounds of Claim 1 of the formula

$R_1NHCHR_2C(O)X$ **Ip**

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or -C(O)R_3.
R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,
R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group,
P_2 is an α-amino acid of Groups E and F,
P_3 is an α-amino acid of Groups E and F,
R_2 is the residue of an α-amino acid of Groups E and F.

33. A compound of Claim 32, said compound being
CBZ-Val-Val-Phe-[C(O)H].

34. Compounds of Claim 1 of the formula
$R_1NHCHR_2C(O)X$ **Iq**
the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is H or -C(O)R_3,
R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,
R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group,
P_2 is Gly,
P_3 is an α-amino acid of Group F or is deleted, and
R_2 is Gly.

35. A compound of Claim 34, said compound being
Tyr-Gly-Gly[C(O)H]
Tyr-Gly-Gly[C(O)OH].

36. Compounds of Claim 1 of the formula
$R_1NHCHR_2C(O)X$ **Ir**
the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is H or -C(O)R_3,
R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,
R_1 is P_2 or P_2 P_g, P_g being a Group K protecting group,
and P_2 is an α-amino acid of Group E,
R_2 is the residue of an α-amino acid of Groups E and G.

37. A compound of Claim 36, said compound being
MeOSuc-Ala-Ala-[C(O)Et].

38. Compounds of Claim 1 of the formula
$R_1NHCHR_2C(O)X$ **Is**
the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is H or -C(O)R_3,
R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,
R_1 is H,
R_2 is the residue of an α-amino acid of Groups A, B, E, F and J.

39. A compound of Claim 38, said compound being
H-Leu[C(O)CH3],
H-Val[C(O)CH3],
H-Arg[C(O)H],
H-Arg[C(O)CH3].

40. Compounds of Claim 1 of the formula
$R_1NHCHR_2C(O)X$ **It**
the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is H or -C(O)R_3,
R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,
R_1 is P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group,
P_2 is an α-amino acid of Groups E and F,
P_3 is an α-amino acid of Groups C, E and F,
R_2 is the residue of an α-amino acid of Group A.

41. A compound of Claim 40, said compound being
D-Pro-Phe-Arg[C(O)H],
D-Pro-Phe-Arg[C(O)CH_3].

42. Compounds of Claim 1 of the formula
$R_1NHCHR_2C(O)X$ **Iu**
the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is H or -C(O)R_3,

R_3 is H, methy, ethyl, OH, methoxy or ethoxy,
R_1 is a Group K protecting group, P_2P_3 or $P_2P_3P_g$, P_g being a Group K protecting group,
P_2 is an α-amino acid of Groups E and F,
P_3 is deleted or is an α-amino acid of Groups B, E or F,
R_2 is H, the residue of an α-amino acid of Groups E, F and J or -A-Si-$R_7R_8R_9$, C_{1-7} alkyl, benzyl phenethyl, or naphthyl.

43. A compound of Claim 42, said compound being
Ac-Ala-Lys[$C(O)OCH_3$],
CBZ-Phe-[$C(O)CH_3$],
CBZ-Val-Phe-[$C(O)OCH_3$],
CBZ-Val-Phe-[$C(O)CH_3$],
CBZ-Val-Phe-[C(O)Et].

44. Compounds of Claim 1 of the formula

$R_1NHCHR_2C(O)X$ Iv

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is H or -$C(O)R_3$,
R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,
R_1 is $P_2P_3P_4$ or $P_2P_3P_4P_g$, P_g being a Group K protecting group,
P_2 is an α-amino acid of Groups C′, E′, F′ and G′,
P_3 is an α-amino acid of Groups C′, E′, F′ and G′,
P_4 is an α-amino acid of Group C′, β-Ala or β-Val,
R_2 is the residue of an α-amino acid of Groups F′ and E′ or cyclohexylmethyl.

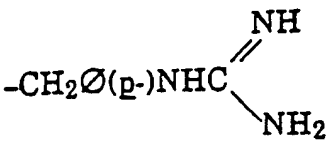
45. A compound of Claim 44, said compound being
Ser-Gln-Asn-Tyr[$C(O)OCH_3$],
Ser-Gln-Asn-Phe[$C(O)OCH_3$],
Ser-Leu-Asn-Tyr[$C(O)OCH_3$],
Ser-Leu-Asn-Phe[$C(O)OCH_3$],
Ser-Gln-Asn-Tyr[$C(O)CH_3$],
Ser-Gln-Asn-Phe[$C(O)CH_3$],
Ser-Leu-Asn-Tyr[$C(O)CH_3$],
Ser-Leu-Asn-Phe[$C(O)CH_3$].

46. A process for preparing compounds of the formulae

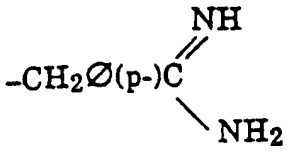
$R_1NHCHR_2C(O)X$
and
$R_1NHCHR_2CH(OH)X$ I

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein
X is H, CHO, $C(O)R_3$, $C(O)OR_3$ or COOH, and
R_1 is H, a Group K protecting group, an α-amino acid, a peptide comprised of 2 to 4 α-amino acids, an α-amino acid bearing a Group K protecting group, or a peptide comprised of 2 to 4 α-amino acids the terminal α-amino acid of which bears a Group K protecting group,
R_2 is the residue of an α-amino acid, C_{1-10} alkyl, aralkyl, aryl or -A-$SiR_7R_8R_9$,
A is a C_{1-6} alkylene, each of
R_7, R_8 and R_9 are C_{1-10} alkyl, benzyl or phenethyl,
R_3 is H, methyl, ethyl, OH, methoxy or ethoxy, the said groups of α-amino acids and Group K protecting groups being defined as
A; Lys and Arg
B: Glu, Asp
C: Ser, Thr, Gln, Asn, Cys, His, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, and N-methyl derivatives
C′: Ser, Thr, Gln, Asn and Cys, and their N-methyl derivatives
D: Pro, Ind
E: Ala, β-Ala, Leu, Ile, Val, n-Val, β-Val, Met, β-Valine, β-Alanine, n-Leu and n-methyl derivatives (β-representing beta)
E′: Leu, Ile, n-Val, Met, n-Leu, CHM and their N-methyl derivatives
F: Phe, Tyr, O-Methyl Tyrosine, (3-pyrazolyl)Ala, (4-pyrimidinyl)Ala, Trp, Nal(1), and N-methyl derivatives
F′: Phe, Tyr, O-methyltyrosine, Trp, Nal-(l) and their N-methyl derivatives.
G: Gly, Sar
G′: Gly

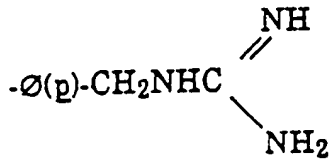
J:



(J-1)

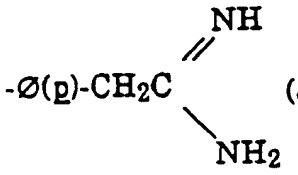


(J-2)



(J-3)

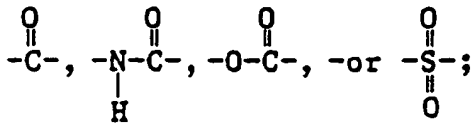
and



(J-4)

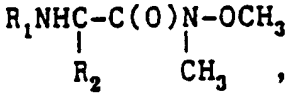
K: Acetyl (Ac), Succinyl (Suc), Methoxysuccinyl (H_3COSuc), Benzoyl (Bz), t-Butyloxycarbonyl (Boc), Carbobenzoxy (CBZ), Tosyl (Ts), Dansyl (DNS), Iso-valeryl (Iva), Methoxysuccinyl (MeOSuc), 1-Adamantanesulphonyl ($AdSO_2$), 1-Adamantaneacetyl (AdAc), 2-Carboxybenzoyl (2-CBZ), Phenylacetyl, t-Butylacetyl (Tba), bis [(1-naphthyl)methyl]acetyl (BNMA), or K'

K': is -A-Rz wherein A is

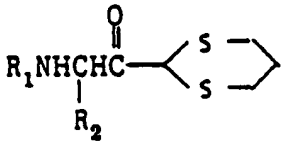


and Rz is an aryl group containing 6, 10 or 12 carbons suitably substituted by 1 to 3 members selected independently form the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, alkyl containing from 1 to 6 carbons, alkoxy containing from 1 to 6 carbons, carboxy, alkylcarbonylamino wherein the alkyl group contains 1 to 6 carbons, 5-tetrazolo, and acylsulfonamido containing from 1 to 15 carbons, provided that when the acylsulfonamido contains an aryl the aryl may be further substituted by a member selected from fluoro, chloro, bromo, iodo and nitro, which comprises

(1) in the instance wherein X is H, chemically reducing a compound of the formula



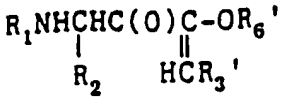
(2) in the instance wherein X is CHO, hydrolizing a thioketal derivative of the formula



(3) in the instance wherein X is $C(O)R_3$, hydrolizing a compound of the formula

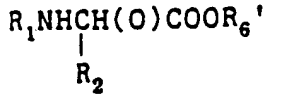
by treatment with a strong acid, R_3'' being methyl or ethyl,

(4) in the instance wherein X is $C(O)OR_3$, subjecting a compound of the formula



wherein R_6' is methyl or ethyl and R_3' is H or methyl, to ozonolysis by treatment with ozone, followed by treating the *in situ* formed ozonide with dimethylsulfide, and

(5) in the instance wherein X is COOH, hydrolizing a compound of the formula



R_6' being methyl or ethyl, by an acid or base catalyzed de-esterification procedure.

47. A compound according to anyone of claims 1 to 45 for use as pharmaceutically active compound .

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(12) EUROPEAN PATENT APPLICATION

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(54) Novel peptidase inhibitors.

(57) This invention relates to analogs of peptidase substrates in which the nitrogen atom of the scissile amide gorup of the substrate peptide has been replaced by H or a substituted carbonyl moiety.

The contemplated peptidase inhibitors of the foregoing enzymes are selected from the generic formula

$R_1NHCHR_2C(O)X$

the hydrates, isosteres or the pharmaceutically acceptable salts thereof, wherein

X is H or $C(O)R_3$,

R_3 is H, methyl, ethyl, OH, methoxy or ethoxy,

R_1 is H, a protecting group, an α-amino acid or a peptide having 2 to 4 α-amino acids, optionally bearing a protecting group,

R_2 is a residue of an α-amino acid responsible for directing the inhibitor to the active site of the enzyme or is $-A-SiR_7R_8R_9$, C_{1-10} alkyl, aralkyl or aryl, with A being a C_{1-6} alkylene, and each of R_7, R_8 and R_9 being C_{1-10} alkyl, benzyl or phenethyl. These analogs of the peptidase substrates provide specific enzyme inhibitors for a variety of proteases, the inhibition of which will have useful physiological consequences in a variety of disease states.

EP 0 363 284 A3

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	EP-A-0 133 225 (HOFFMANN-LA ROCHE) * Whole document * ---	1,47	C 07 K 5/02 C 07 K 5/06 C 07 K 5/08 C 07 K 5/10 C 07 C 271/10 A 61 K 37/64
X	EP-A-0 128 762 (SANKYO) * Whole document * ---	1,47	
X	EP-A-0 126 009 (CNRS) * Example 3; pages 8-9; claims * ---	1,2-5, 47	
X	EP-A-0 124 317 (ICI) * Whole document * ---	1,2-5, 47	
X	WO-A-8 404 301 (NATL. RES. DEV. CORP.) * Whole document * ---	1,47	
X	WO-A-8 400 365 (NATL. RES. DEV. CORP.) * Whole document, especially table 1, compounds 7-9 * ---	1,8-9, 42-43, 47	
X	DE-A-3 000 225 (RICHTER) * Whole document * ---	1,6-7, 47	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
X	AU-B- 19 392 (ZAIDAN HOJIN) * Whole document * ---	1,16-17 ,47	C 07 K C 07 C A 61 K
X	FR-A-2 490 632 (NIPPON KAYAKU K.K.) * Whole document * --- -/-	1,6-7, 10-11, 14-17, 22-23, 28-29, 40-41,	

The present search report has been drawn up for all claims

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THE HAGUE	19-03-1992	MASTURZO P.

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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid,

namely claims:

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions,
namely:

see sheet -B-

☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid,

namely claims:

☐ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims,

namely claims:

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DOCUMENTS CONSIDERED TO BE RELEVANT

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X	CHEMICAL ABSTRACTS, vol. 105, no. 3, 21st July 1986, page 676, abstract no. 24605p, Columbus, Ohio, US; J.A. FEHRENTS et al.: "Synthesis of aldehydic peptides inhibiting renin", & INT. J. PEPT. PROTEIN RES. 1985, 26(3), 236-41 * Abstract * ---	1-3,8-9 ,28-33, 42,47	
X	CHEMICAL ABSTRACTS, vol. 104, no. 15, 14th April 1986, page 312, abstract no. 125573m, Columbus, Ohio, US; G.C. SZABO et al.: "Specific inhibition of human granulocyte elastase with peptide aldehydes", & FEBS LETT. 1986, 195(1-2), 265-8 * Abstract * ---	1-5,8-9 ,47	
X	CHEMICAL ABSTRACTS, vol. 101, no. 21, 19th November 1984, page 818, abstract no. 192438x, Columbus, Ohio, US; I.J. GALPIN et al.: "Synthetic analogs of the proteinase inhibitor: chymostatin", INT. J. PEPT. PROTEIN RES. 1984, 23(5), 477-86 * Abstract * ---	1,47	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
X	CHEMICAL ABSTRACTS, vol. 100, no. 25, 18th June 1984, page 227, abstract no. 205401m, Columbus, Ohio, US; K.A. KOZLOWSKI et al.: "Tumor cell proteinase visualization and quantification using a fluorescent transition-state analog probe", & PROC. NATL. ACAD. SCI. U.S.A. 1984, 81(4), 1135-9 * Abstract * --- -/-	1,6-7, 47	

The present search report has been drawn up for all claims

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X	CHEMICAL ABSTRACTS, vol. 100, no. 23, 4th June 1984, page 250, abstract no. 187896v, Columbus, Ohio, US; J.A. FEHRENTZ et al.: "Aldehydic peptides inhibiting renin", & FEBS LETT. 1984, 167(2), 273-6 * Abstract * ---	1,47	
X	CHEMICAL ABSTRACTS, vol. 100, no. 15, 9th April 1984, page 37, abstract no. 114752k, Columbus, Ohio, US; D. BAGDY et al.: "In vitro and ex vivo effect of tripeptide aldehydes on blood coagulation", & KISERL. ORVOSTUD. 1983, 35(6), 650-61 * Abstract * ---	1,6-7, 10-11, 47	
X	CHEMICAL ABSTRACTS, vol. 100, no. 3, 16th January 1984, page 242, abstract no. 19717u, Columbus, Ohio, US; I.J. GALPIN et al.: "Analogs of chymostatin", & PEPT. PROC. EUR. PEPT. SYMP., 17th 1982, 649-52 * Abstract * ---	1,47	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
X	CHEMICAL ABSTRACTS, vol. 97, no. 3, 19th July 1982, page 339, abstract no. 19651n, Columbus, Ohio, US; S. BAJUSZ et al.: "Structure-activity relationships among the tripeptide aldehyde inhibitors of plasmin and thrombin", & PEPT. SYNTH., STRUCT., FUNCT., PROC. AM. PEPT. SYMP., 7th 1981, 417-20 * Abstract * --- -/-	1,6-7, 10-11, 47	

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X	CHEMICAL ABSTRACTS, vol. 90, no. 13, 26th March 1979, pages 188-189, abstract no. 99132n, Columbus, Ohio, US; S. BAJUSZ et al.: "Inhibition of thrombin and trypsin by tripeptide aldehydes", & INT. J. PROTEIN RES. 1978, 12(4), 217-21 * Abstract * ---	1,6-7, 10-11, 47	
X	CHEMICAL ABSTRACTS, vol. 87, no. 25, 19th December 1977, page 278, abstract no. 196211h, Columbus, Ohio, US; R.C. THOMPSON et al.: "Peptide aldehydes: potent inhibitors of serine and cysteine proteases", & METHODS ENZYMOL. 1977, 46, (AFFINITY LABELING), 220-5 * Abstract * ---	1,46-47	
X	CHEMICAL ABSTRACTS, vol. 86, no. 1, 3rd January 1977, page 511, abstract no. 5859x, Columbus, Ohio, US; & HU-A-12 214 (GYOGYSZERKUTATO INTEZET) 28-09-1976 * Abstract * ---	1,6-7, 10-11, 47	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
X	CHEMICAL ABSTRACTS, vol. 85, no. 15, 11th October 1976, page 235, abstract no. 105947x, Columbus, Ohio, US; S. BAJUSZ et al.: "Peptide aldehyde inhibitors of the fibrinogen-thrombin reaction", & PEPT.: CHEM., STRUCT. BIOL., PROC. AM. PEPT. SYMP., 4th 1975, 603-8 * Abstract * --- -/-	1,6-7, 10-11, 47	

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X	CHEMICAL ABSTRACTS, vol. 80, no. 25, 24th June 1974, page 481, abstract no. 146554g, Columbus, Ohio, US; & JP-A-73 91 028 (SANKYO CO., LTD) 27-11-1973 * Abstract * ---	1,8-9, 47	
X	BIOCHEMISTRY, vol. 27, no. 17, 23rd August 1988, pages 6568-6573, American Chemical Society; R.A. SMITH et al.: "Inhibition of cathepsin B by peptidyl aldehydes and ketones: Slow-binding behavior of a trifluoromethyl ketone" * Whole article, especially table 1 * ---	1,47	
X	BIOCHEMISTRY, vol. 25, no. 5, 11th March 1986, pages 1072-1078, American Chemical Society; D. GROBELNY et al.: "Inhibition of angiotensin converting enzyme by aldehyde and ketone substrate analogues" * Whole article, especially table 1 * ---	1,47	
X	BIOCHEMISTRY, vol. 18, no. 8, 17th April 1979, pages 1552-1558, American Chemical Society; R.C. THOMPSON et al.: "Reaction of peptide aldehydes with serine protease. Implications for the entropy changes associated with enzymatic catalysis" * Whole article, especially table 1 * --- -/-	1,47	

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X	PEPTIDES, STRUCTURE & FUNCTION - PROCEEDINGS OF THE AMERICAN PEPTIDE SYMPOSIUM, 1985, pages 799-802, Pierce Chemical Co., Rockford, US; I.J. GALPIN et al.: "A new approach to the synthesis of peptide aldehyde inhibitors" * Whole article * ---	1,47	
P,X	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 157, no. 3, 30th December 1988, pages 1117-1123, Academic Press, Duluth, MN, US; S. MEHDI et al.: "Inhibition of the proteolysis of rat erythrocyte membrane proteins by a synthetic inhibitor of calpain" * Whole article * ---	1,47	
P,X	EP-A-0 335 572 (BEHRINGWERKE) * Whole document, especially page 5, example 2; page 7, claim 1 * ---	1,47	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
X	EP-A-0 281 316 (YAMANOUCHI) * Whole document, especially the examples 12-27,33 * ---	1,24,30 ,46-47	
X	EP-A-0 266 950 (PFIZER) * Whole document, especially page 3, formula 2 * ---	1,24,30 ,46-47	
X	EP-A-0 264 106 (BANYU) * Whole document, especially compounds having the structure III on page 6 and claim 5, pages 41-42 * --- -/-	1,24,30 ,46-47	

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X	EP-A-0 195 212 (MERRELL DOW) * Whole document * ---	1-24,30,46-47	
X	EP-A-0 189 203 (ABBOTT) * Examples 6,7 * ---	1-30,32,34-36,38-42,44,46-47	
X	PEPTIDES, STRUCTURE & FUNCTION (C.M. DEBER et al.) - PROCEEDINGS OF THE AMERICAN PEPTIDE SYMPOSIUM, 1985, pages 819-822, Pierce Chemical Co., Rockford, US; H. HORI et al.: "Inhibition of human leukocyte elastase, porcine pancreatic elastase and cathepsin G by peptide ketones" * Whole document, especially table 1, compounds 7-11 * ---	1-30,32,34-36,38-42,44,46-47	
X	CHEMICAL ABSTRACTS, vol. 107, no. 25, 21st December 1987, page 21, abstract no. 228458u, Columbus, Ohio, US; J.L. KRAUS et al.: "Effect of new biologically active polypeptides on dihexadecyl phosphate vesicles", & PHARMACOL. RES. COMMUN. 1987, 19(7), 469-77 * Abstract * --- -/-	1	TECHNICAL FIELDS SEARCHED (Int. Cl.5)

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X	TETRAHEDRON LETTERS, vol. 29, no. 28, 1988, pages 3433-3436, Pergamon Press, Oxford, GB; J.P. BURKHART et al.: "Oxidation of alpha-hydroxy esters to alpha-keto esters using the dess-martin periodinane reagent" * Whole document, especially the table * ---	1,46-47	
P,X	THE JOURNAL OF ORGANIC CHEMISTRY, vol. 54, no. 16, 4th August 1989, pages 3913-3916, American Chemical Society; M.R. ANGELASTRO et al.: "An efficient synthesis of novel alpha-diketone and alpha-keto ester derivatives of N-protected amino acids and peptides" * Whole document * ---	1	
P,X	EP-A-0 296 581 (SQUIBB) * Whole document * ---	1	
T	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 166, no. 2, 30th January 1990, pages 595-600, Academic Press, Inc., San Diego, US; S. MEHDI et al.: "The inhibition of human neutrophil elastase and cathepsin G by peptidyl 1,2-dicarbonyl derivatives" * Whole document * -----	1,2,4	TECHNICAL FIELDS SEARCHED (Int. Cl.5)

The present search report has been drawn up for all claims

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LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims 1-30,32,34-36,38-42,44,46-47(partially) and 31,33: Compounds described by the first formula of claim 1, X being H, their hydrates, isosteres and pharmaceutically acceptable salts.

2. Claims 1-30,32,34-36,38-42,44,46-47(partially) and 37,43,45: Compounds described by the first formula of claim 1, X being $C(O)R_3$, where R_3 is as defined in claim 1, their hydrates, isosteres and pharmaceutically acceptable salts.

3. Claims 1,24,30,46-47(partially): Compounds described by the second formula of claim 1, X being H, their hydrates, isosteres and pharmaceutically acceptable salts.

4. Claims 1,24,30,46-47(partially): Compounds described by the second formula of claim 1, X being $C(O)R_3$, where R_3 is as defined in claim 1, their hydrates, isosteres and pharmaceutically acceptable salts.